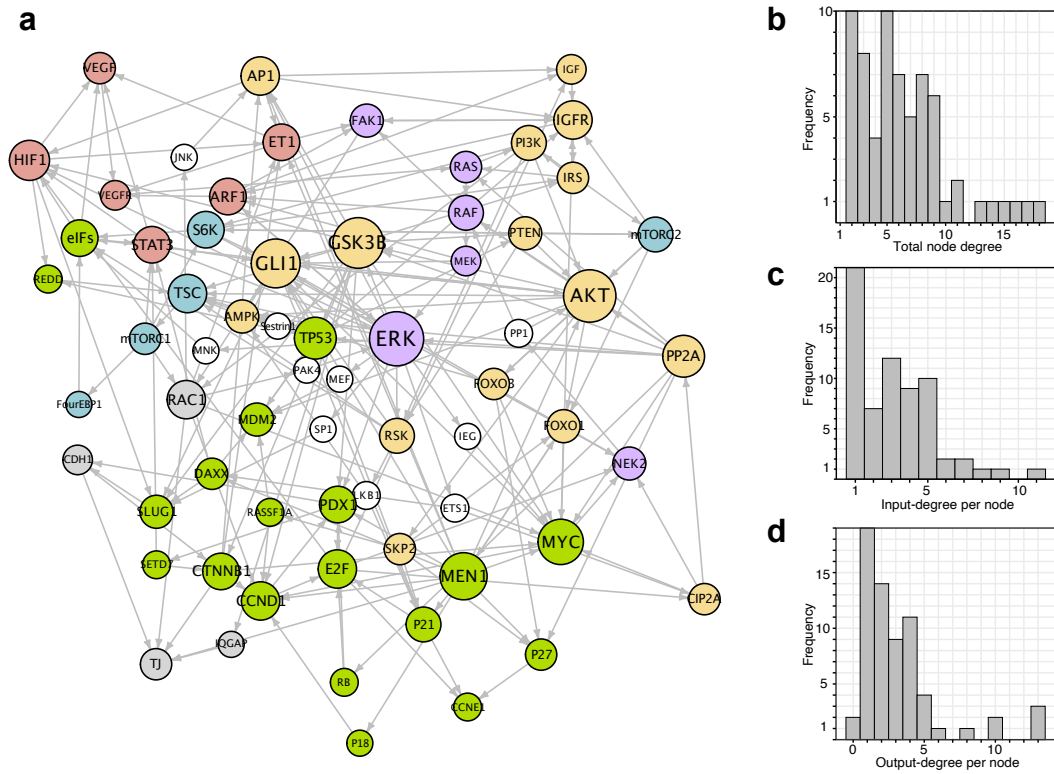


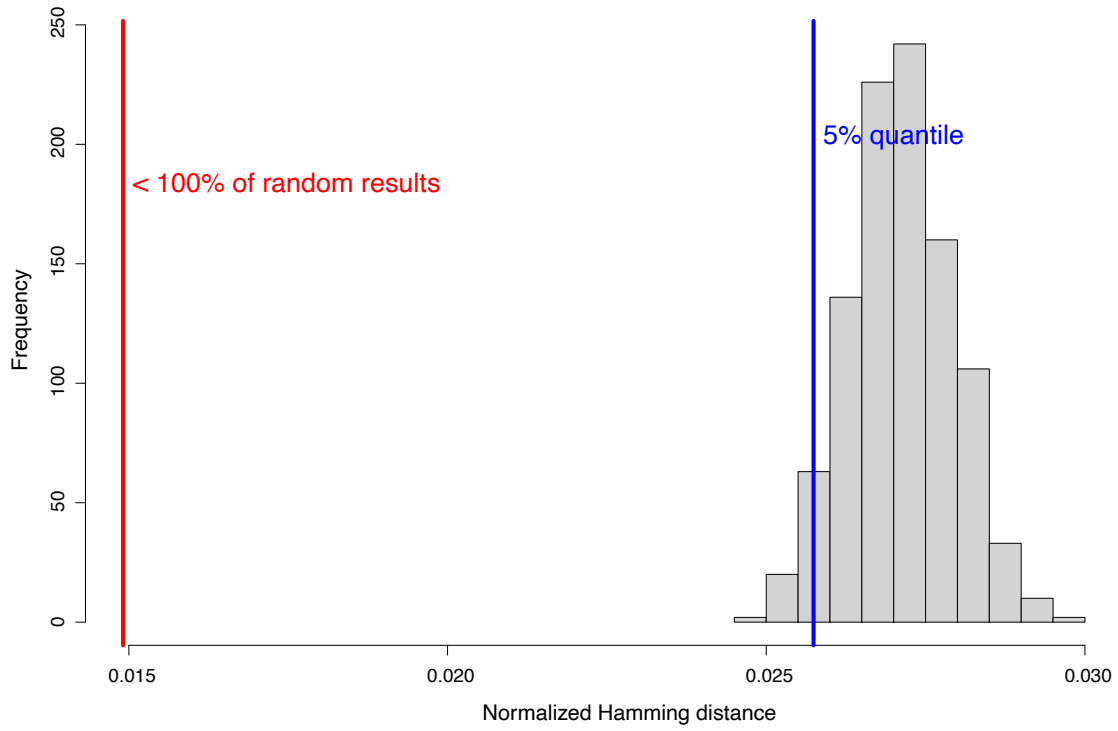
A systems biology approach to define mechanisms, phenotypes, and drivers in PanNETs with a personalized perspective

– Supplementary Information –

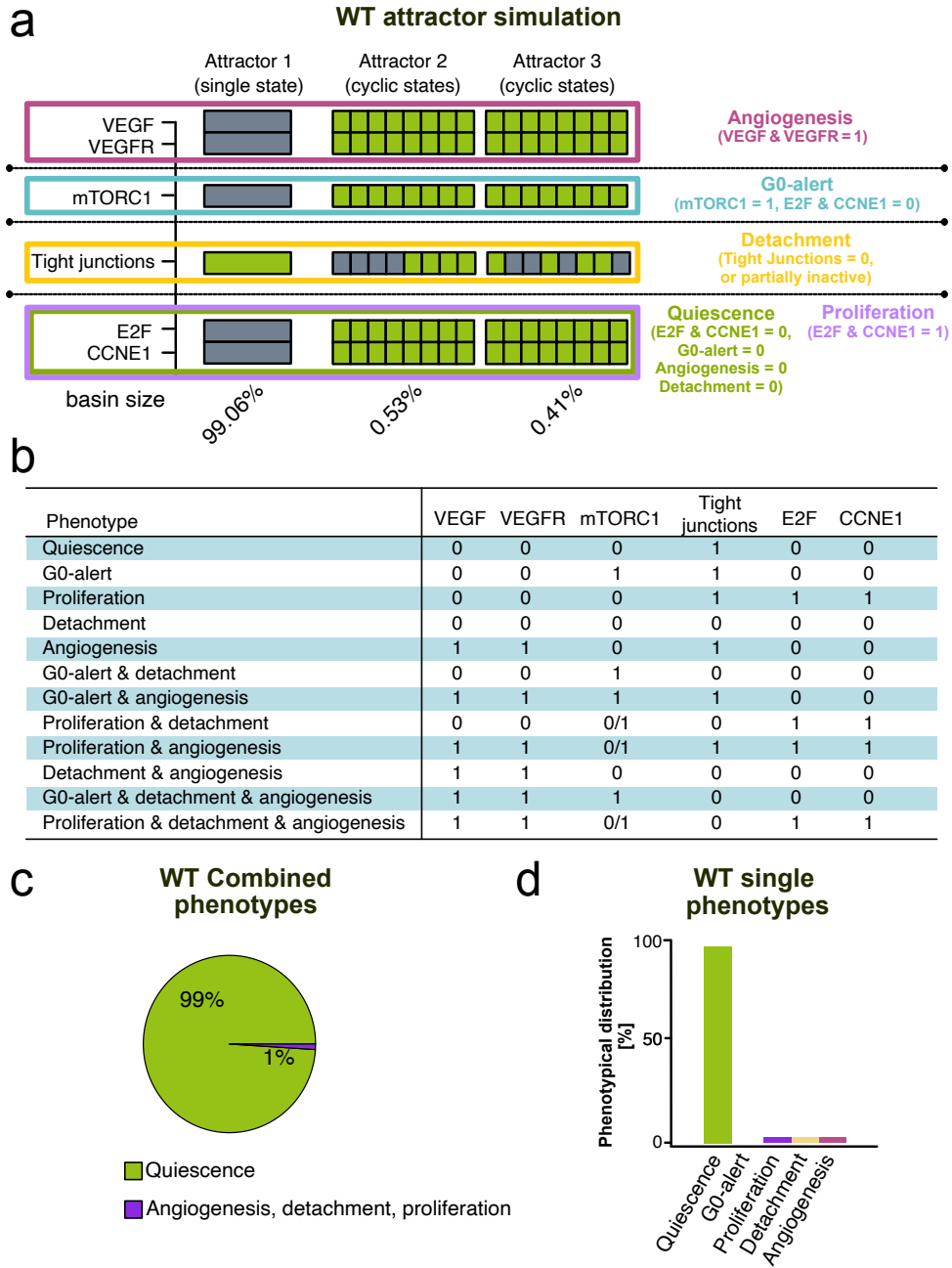
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Annika M. T. U. Kestler¹, Felix M. Weidner¹, Julian D. Schwab¹, Julia Maier^{1,3}, Malte Buchholz⁴,
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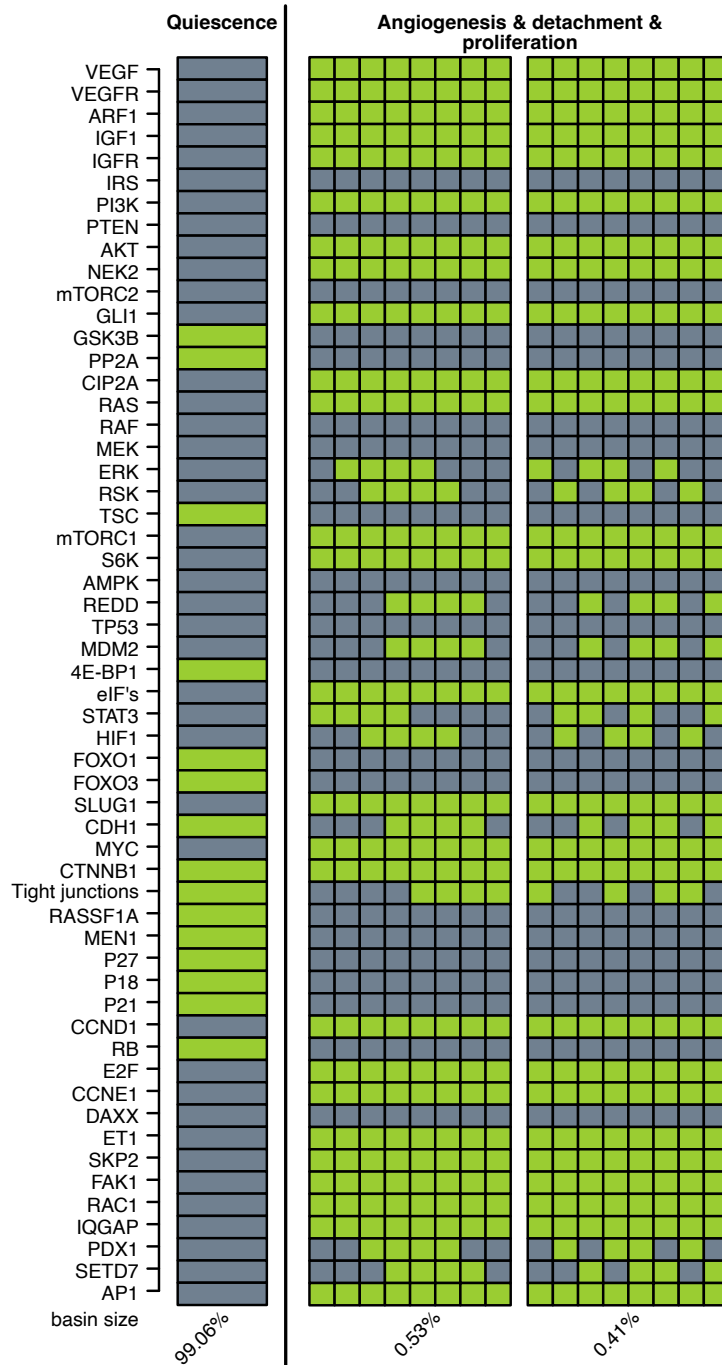
Supplementary Figure 1: Model scale-freeness. (a) Automatically generated interaction graph using the R-package igraph [1]. The node size correlates with the z-score transformed total node degree of the nodes within the PanNET model. Colors depict pathway association - red = angiogenesis; purple = MAPK signaling; yellow = PI3K/AKT signaling; blue = mTORC signaling; grey = cell adhesion; green = cell cycle; white = multiple pathway associations. (b) Total node degree distribution of the PanNET model. (c) Input-degree distribution of the PanNET model. (d) Output-degree distribution of the PanNET model.



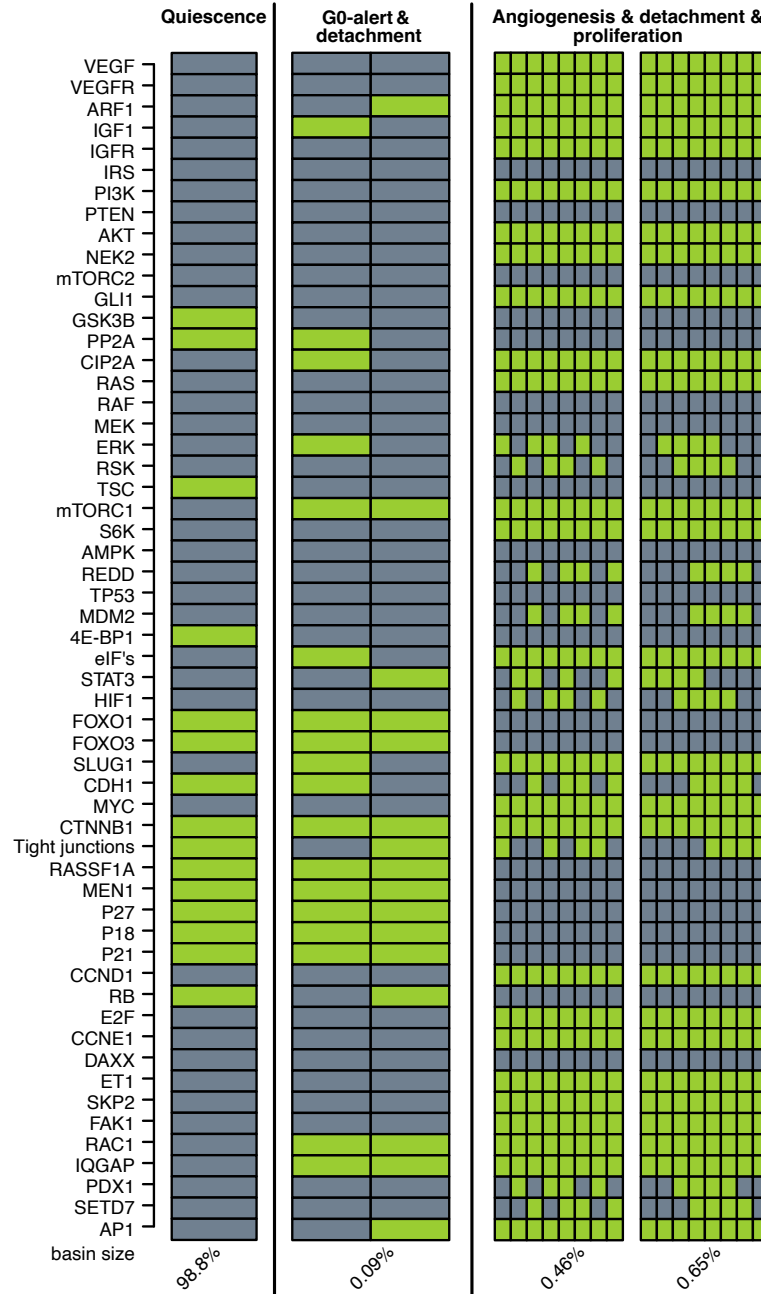
Supplementary Figure 2: Stability assesement of the PanNETs model. One thousand randomly drawn states of the HSC model were mutated by bit flip and their successor states were computed. The successor states of the mutated and the original states were then compared using the normalized Hamming distance (red line, intercept at 0.0149). The same analysis was performed for 1,000 randomly generated networks of the same size (histogram). The blue line shows the 5% quantile (intercept at 0.0257). The calculate p-value between the model and the randomly generated networks is below 0.05. Hence the model is significantly more robust than noise.



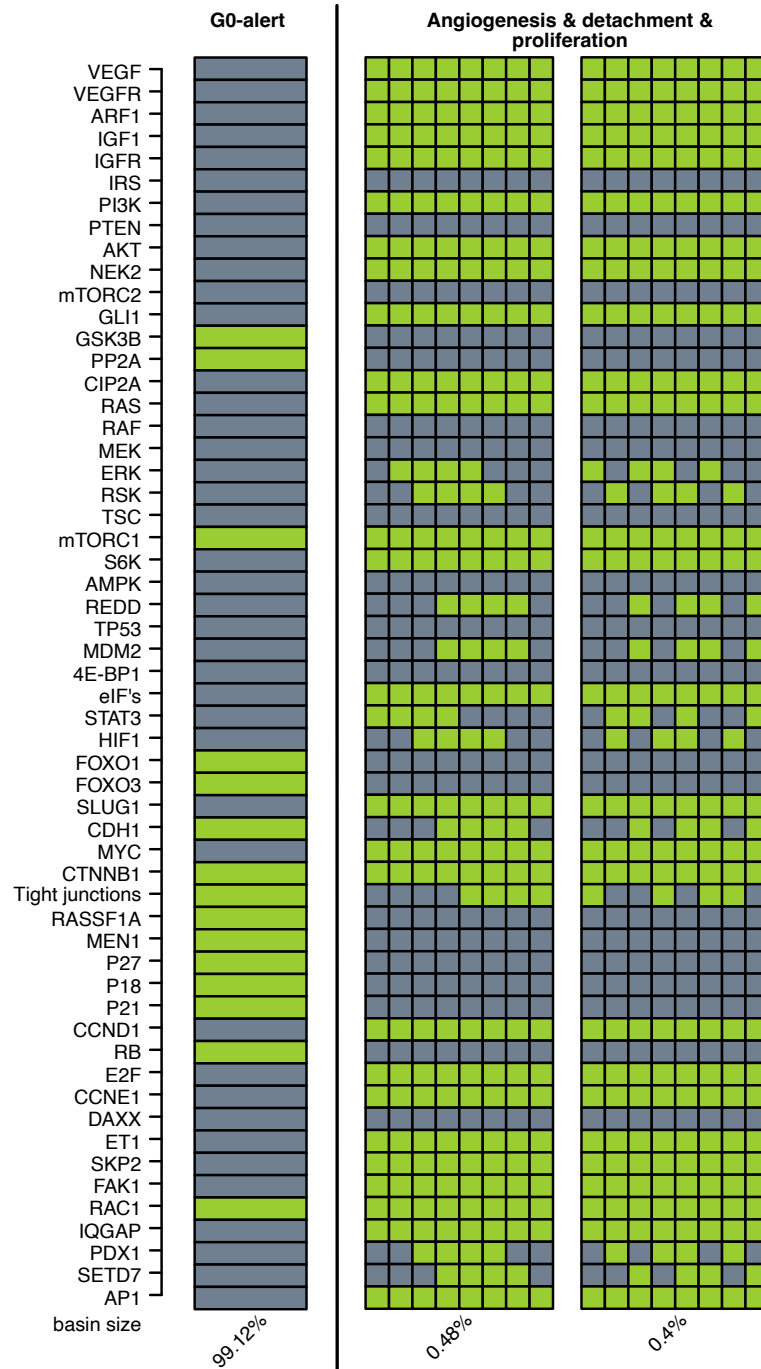
Supplementary Figure 3: Example of attractor interpretation and visualization. The interpretation of read-out phenotypes and their representation is presented based on the WT simulation of the PanNET model. Nodes used to interpret the PanNET model phenotypes are extracted from the attractor pattern (a). On the side of each node, the criteria for assigning the specific phenotypes are reported. The estimated basin sizes are reported under each attractor. In the attractor pattern, green boxes indicate activation, while dark purple ones indicate inactivation. The phenotype encoding is also exhaustively depicted in a tabular form (b). Phenotypes present in each attractor then are combined and weighted based on their basin of attraction (c). In the pie chart, 99% of the phenotype is represented by quiescence, represented by the single state attractor. Instead, the two cyclic attractors cover 1% of the basin connected to angiogenesis, detachment, and proliferation. The two combined phenotypes can be broken down independently into single phenotypes (d). Again percentages for each phenotype overall the attractor landscape corresponds to the estimated basins of attraction. In this case, overall the attractor landscape, 99% is represented by quiescence, while angiogenesis, detachment, and proliferation cover the 1%. This visualisation is considered more intuitive when comparing the effect of many perturbations on the attractor landscape.



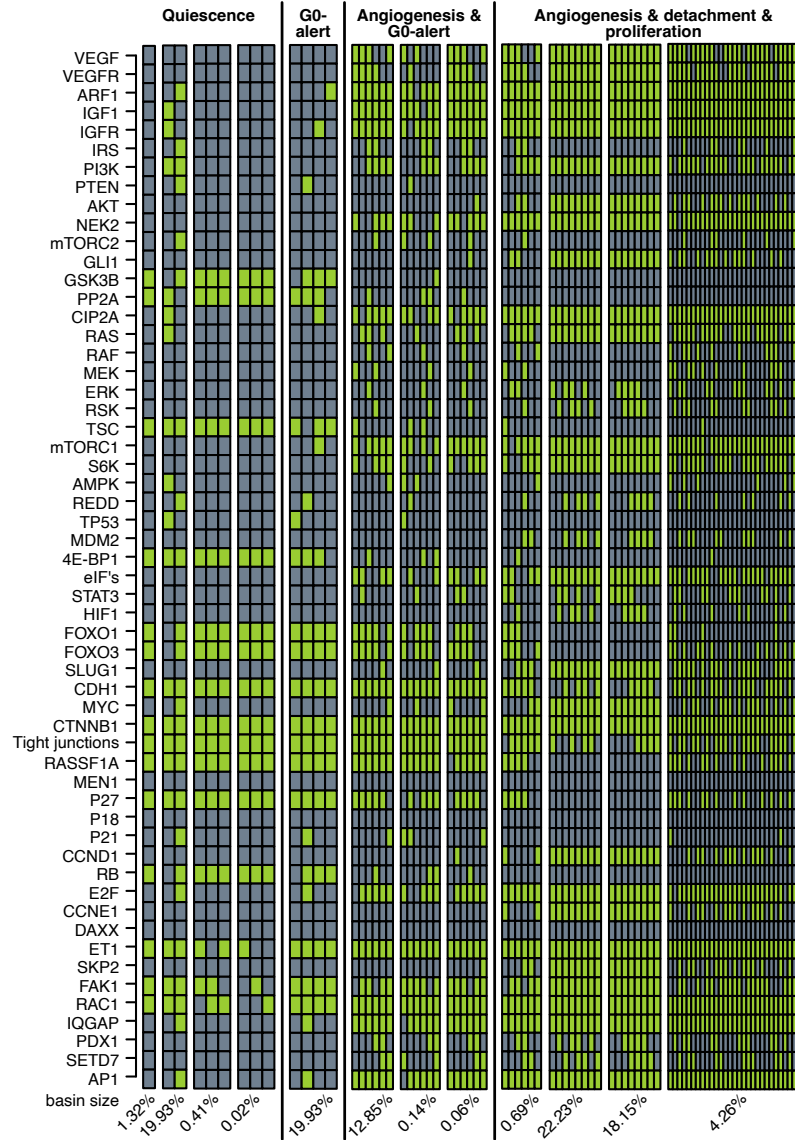
Supplementary Figure 4: Unperturbed attractor patterns of the PanNETs model. The attractor landscape of the unperturbed (WT) PanNETs network is reported. Attractors are grouped based on their matched phenotypes. Below each attractor the basin size is reported. Activities are reported in the colored boxed. Here, green indicates active (1) and grey indicates inactive (0) genes/proteins.



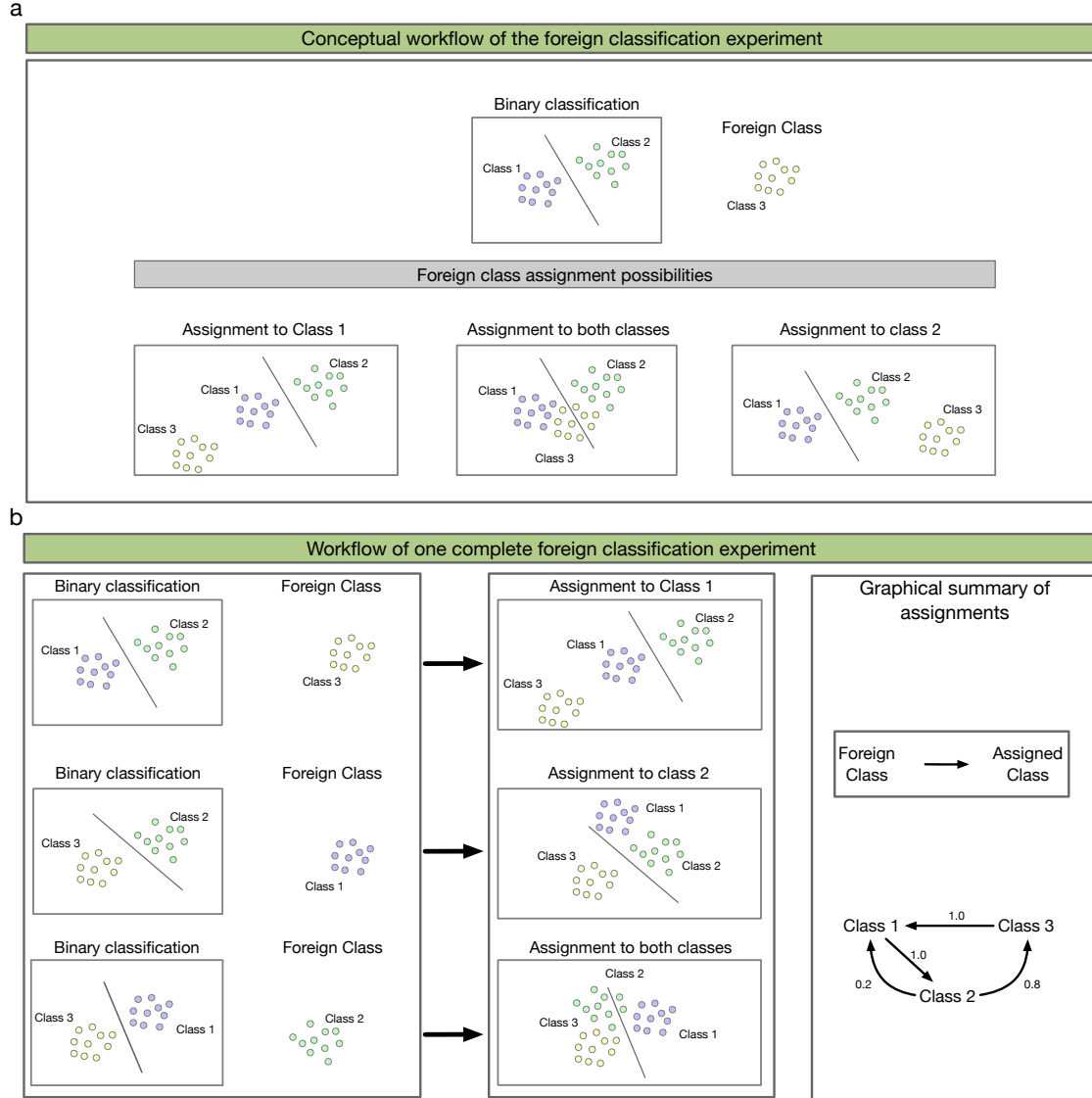
Supplementary Figure 5: DAXX loss attractor patterns of the PanNETs model. The attractor landscape of the DAXX loss (DAXX KO) PanNET network is reported. Attractors are grouped based on their matched phenotypes. Below each attractor the basin size is reported. Activities are reported in the colored boxed. Here, green indicates active (1) and grey indicates inactive (0) genes/proteins.



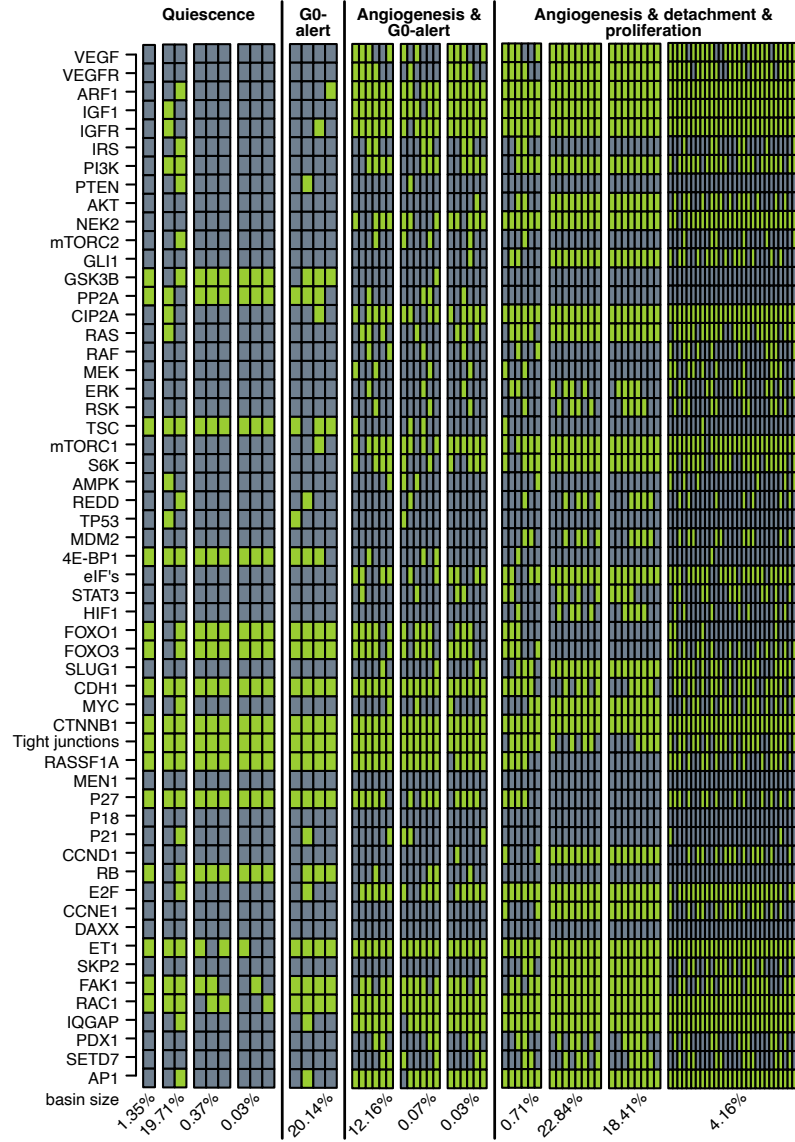
Supplementary Figure 6: TSC loss attractor patterns of the PanNETs model. The attractor landscape of the TSC loss (TSC KO) PanNET network is reported. Attractors are grouped based on their matched phenotypes. Below each attractor the basin size is reported. Activities are reported in the colored boxed. Here, green indicates active (1) and grey indicates inactive (0) genes/proteins.



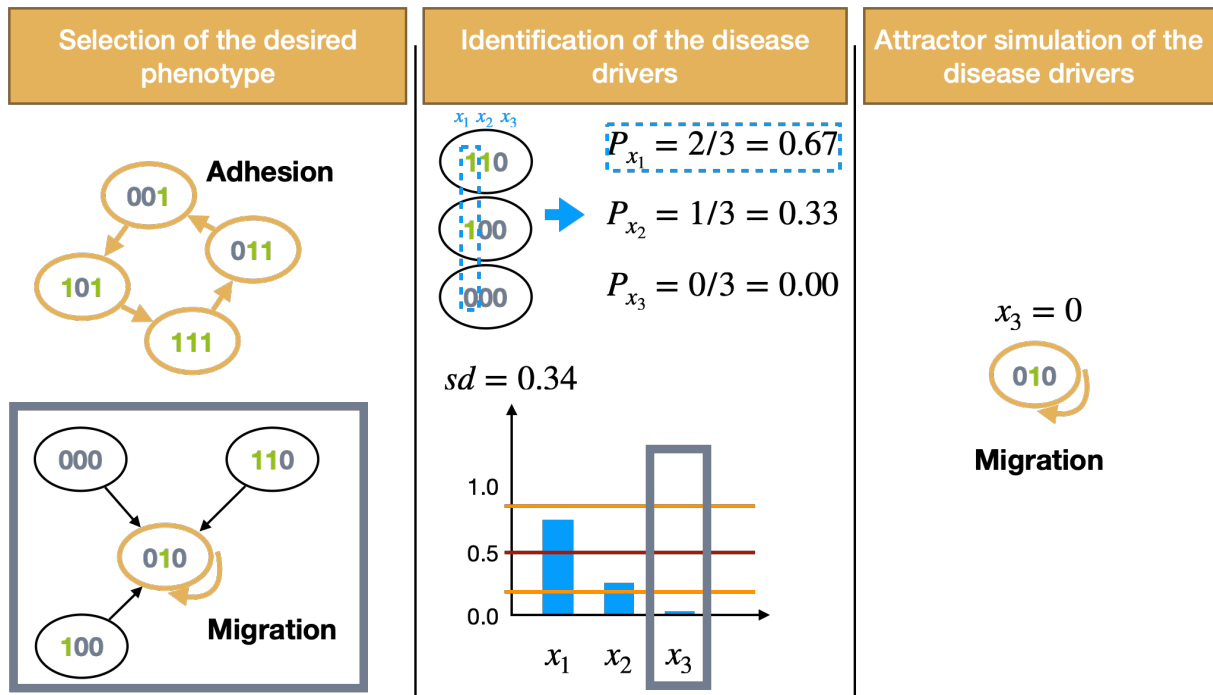
Supplementary Figure 7: MEN1 loss attractor patterns of the PanNETs model. The attractor landscape of the MEN1 loss (MEN1 KO) PanNET network is reported. Attractors are grouped based on their matched phenotypes. Below each attractor the basin size is reported. Activities are reported in the colored boxed. Here, green indicates active (1) and grey indicates inactive (0) genes/proteins.



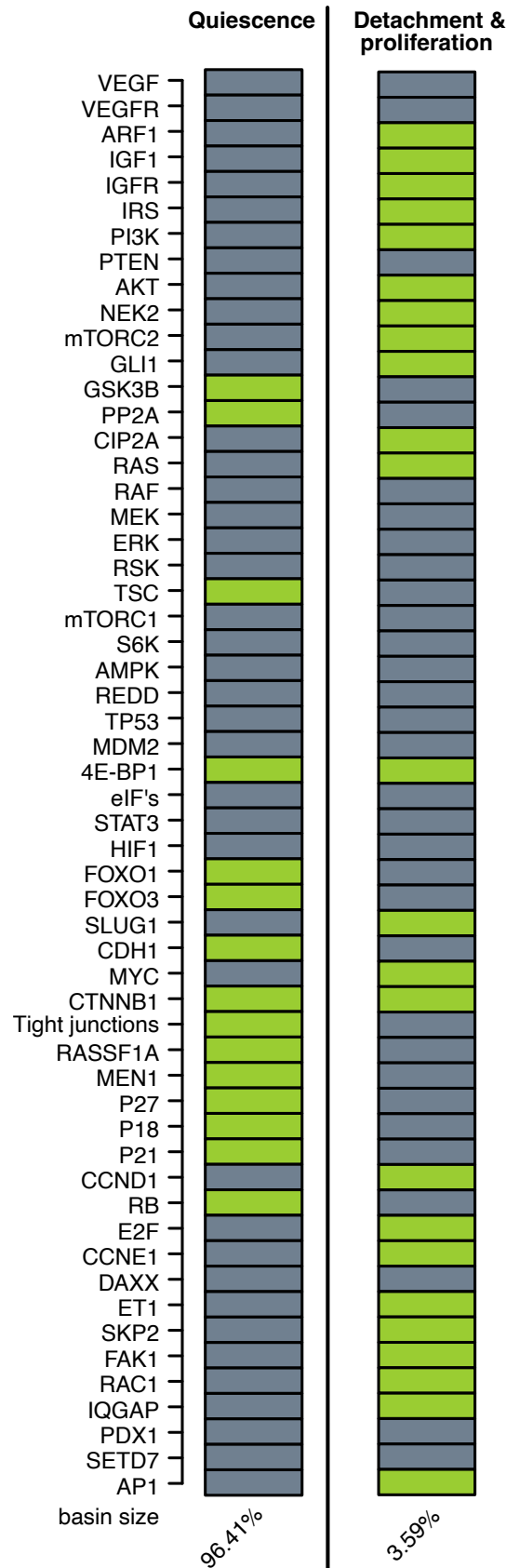
Supplementary Figure 8: Workflow foreign classification. The structure of the foreign classification experiments is depicted. (a). First two classes in a dataset are chosen to perform a linear classification. A third class is left out, and represents the foreign class of the experiment. The latter is assigned to one of the two classes, or both of them, based on the linear classification previously performed (lower panel). The workflow of the of a complete foreign classification experiment is depicted below, in pictorial dataset composed of three classes (b). All classes in the are iteratively used in couples to perform the first binary classification. Each foreign class is assigned based on the the first linear classification. Finally, the results of the experiment are summarized graphically in an interaction graph, where the direction of edges indicates the assignment of the foreign class to its assigned class. Numbers over the edges indicate the assignment fraction of the foreign class in exam.



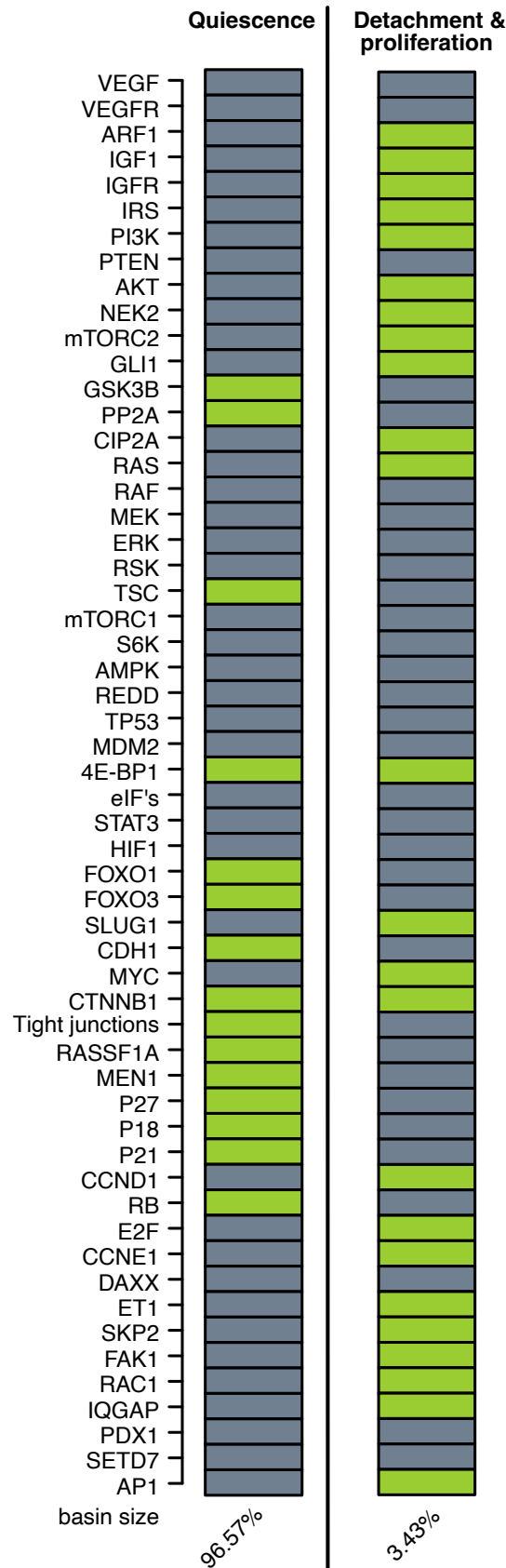
Supplementary Figure 9: MEN1 and DAXX loss attractor patterns of the PanNETs model. The attractor landscape of the MEN1 and DAXX loss (MEN1 & DAXX KO) PanNET network is reported. Attractors are grouped based on their matched phenotypes. Below each attractor the basin size is reported. Activities are reported in the colored boxed. Here, green indicates active (1) and grey indicates inactive (0) genes/proteins.



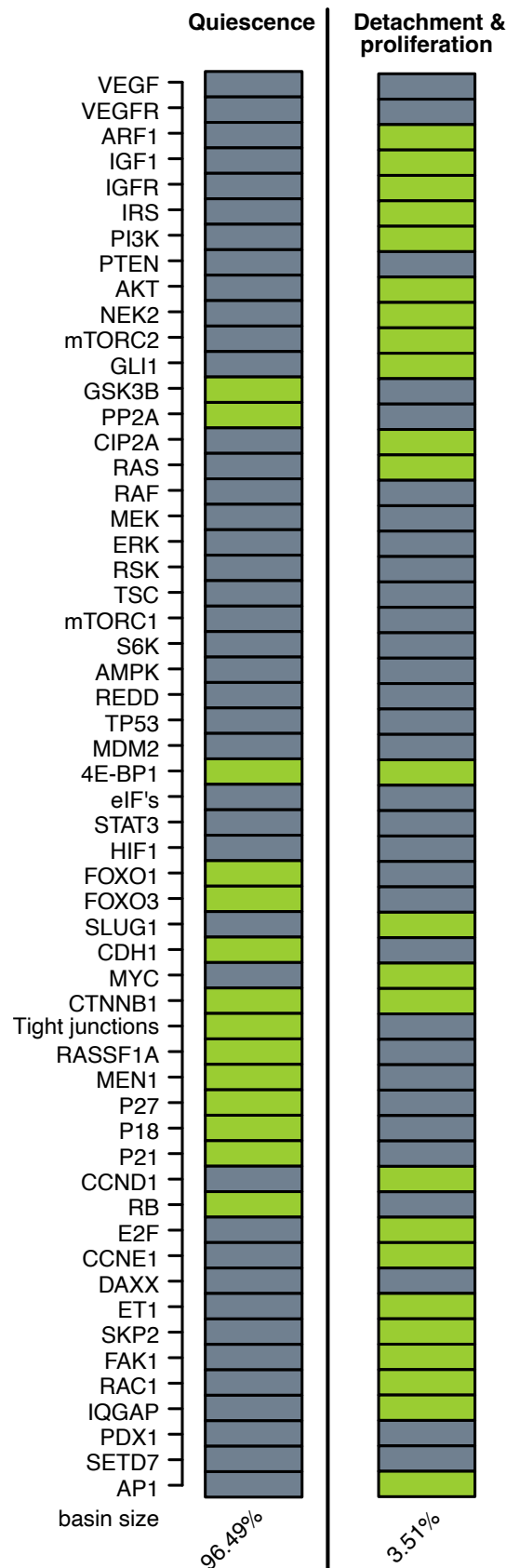
Supplementary Figure 10: Brief visualization for the disease driver screening. A toy model of the disease driver screening strategy is depicted. First an attractor of interest is selected, in this case the migration inducing one (left panel). The basin of attraction of the attractor of interest is then screened and frequency of activities of each node is calculated (middle panel). Then, nodes whose frequency of activities is higher or lower of one standard deviation are selected. Finally, the corresponding perturbation is simulated and the attractor related phenotype is evaluated (right panel).



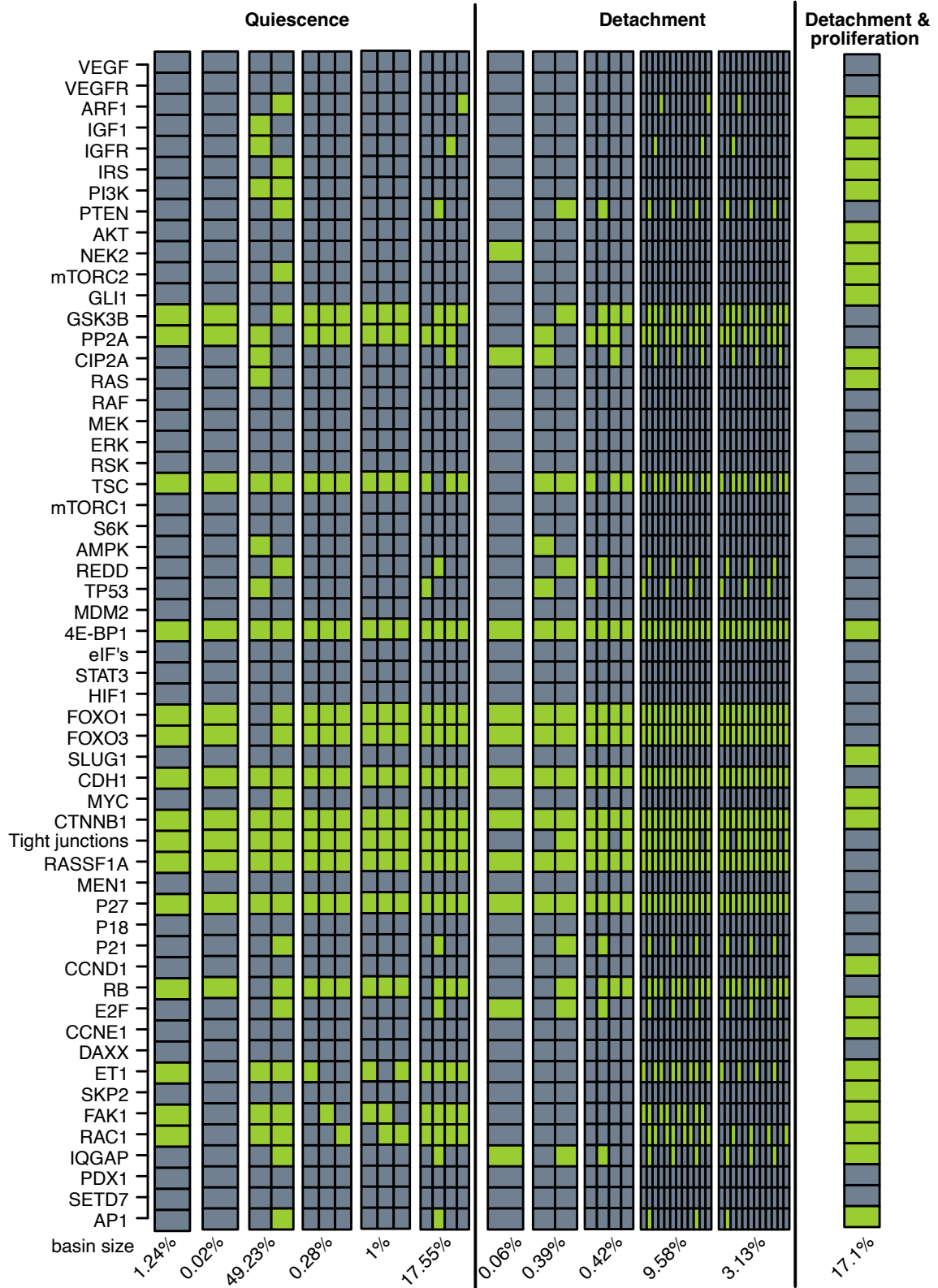
Supplementary Figure 11: mTORC1 intervention attractor patterns in WT PanNETs. The attractor landscape of the mTORC1 intervention on the WT PanNET network is reported. Attractors are grouped based on their matched phenotypes. Below each attractor the basin size is reported. Activities are reported in the colored boxed. Here, green indicates active (1) and grey indicates inactive (0) genes/proteins.



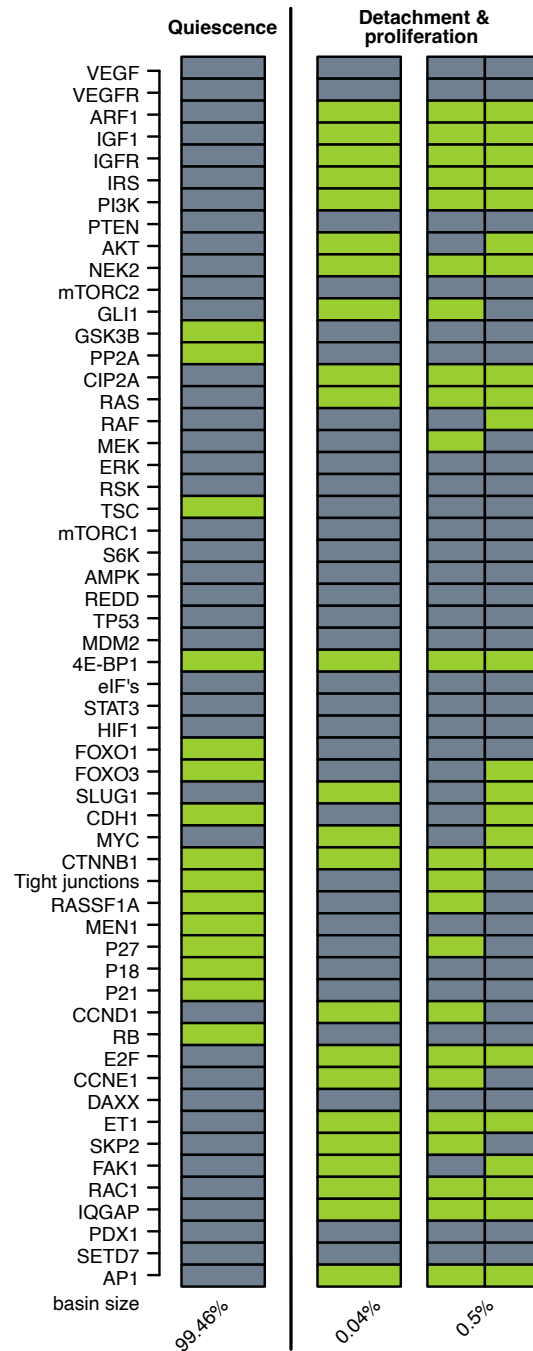
Supplementary Figure 12: mTORC1 intervention attractor patterns in DAXX loss PanNETs. The attractor landscape of the mTORC1 intervention on the DAXX loss PanNET network is reported. Attractors are grouped based on their matched phenotypes. Below each attractor the basin size is reported. Activities are reported in the colored boxed. Here, green indicates active (1) and grey indicates inactive (0) genes/proteins.



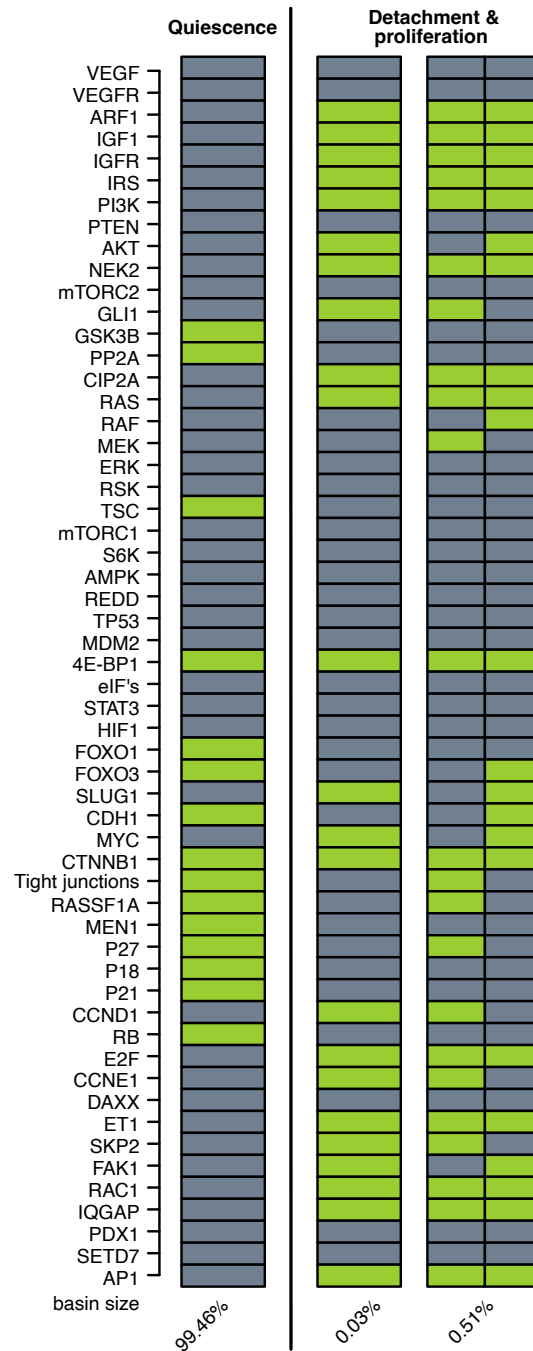
Supplementary Figure 13: mTORC1 intervention attractor patterns in TSC loss PanNETs. The attractor landscape of the mTORC1 intervention on the TSC loss PanNET network is reported. Attractors are grouped based on their matched phenotypes. Below each attractor the basin size is reported. Activities are reported in the colored boxed. Here, green indicates active (1) and grey indicates inactive (0) genes/proteins.



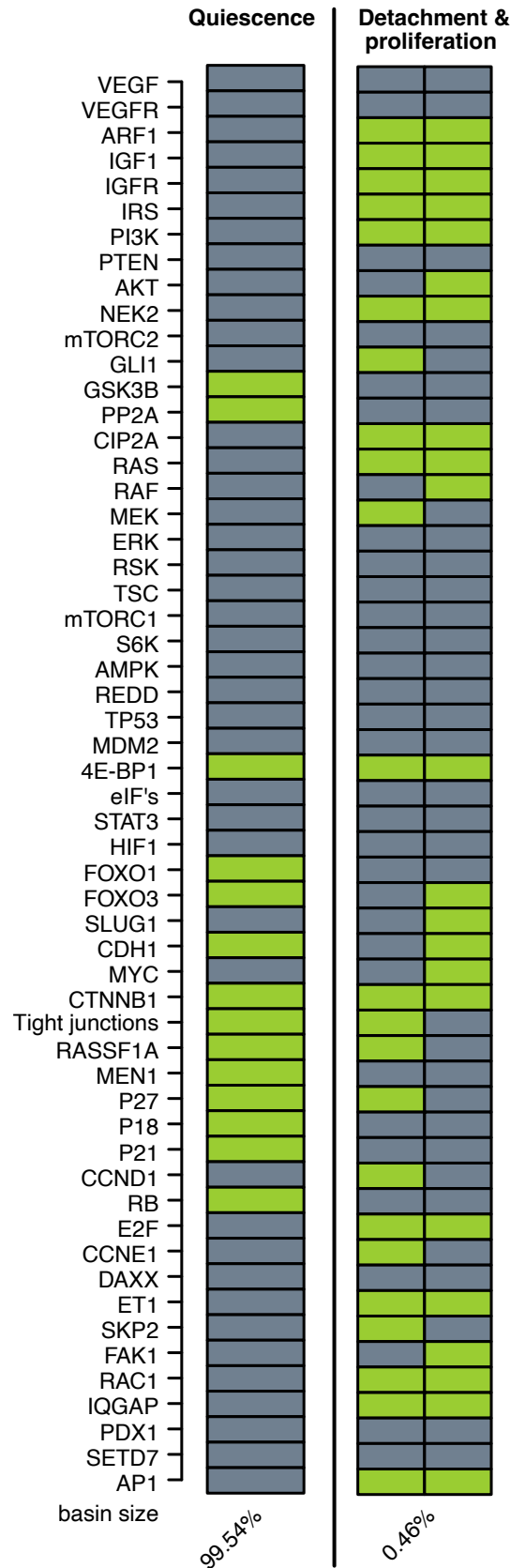
Supplementary Figure 14: mTORC1 intervention attractor patterns in MEN1 loss PanNETs. The attractor landscape of the mTORC1 intervention on the MEN1 loss PanNET network is reported. Attractors are grouped based on their matched phenotypes. Below each attractor the basin size is reported. Activities are reported in the colored boxed. Here, green indicates active (1) and grey indicates inactive (0) genes/proteins.



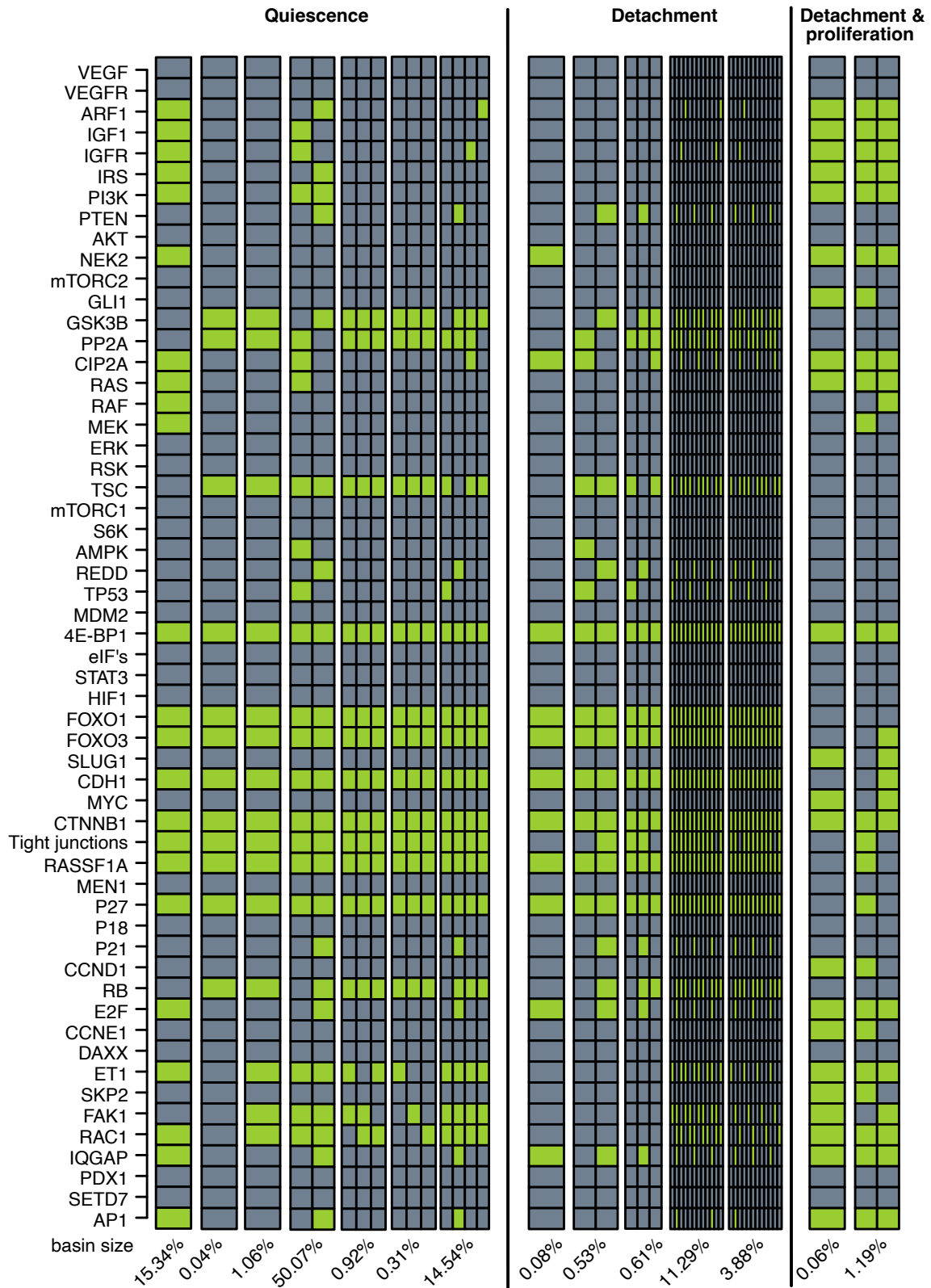
Supplementary Figure 15: mTORC1 and mTORC2 intervention attractor patterns in WT PanNETs. The attractor landscape of the mTORC1 and mTORC2 intervention on the WT PanNET network is reported. Attractors are grouped based on their matched phenotypes. Below each attractor the basin size is reported. Activities are reported in the colored boxed. Here, green indicates active (1) and grey indicates inactive (0) genes/proteins.



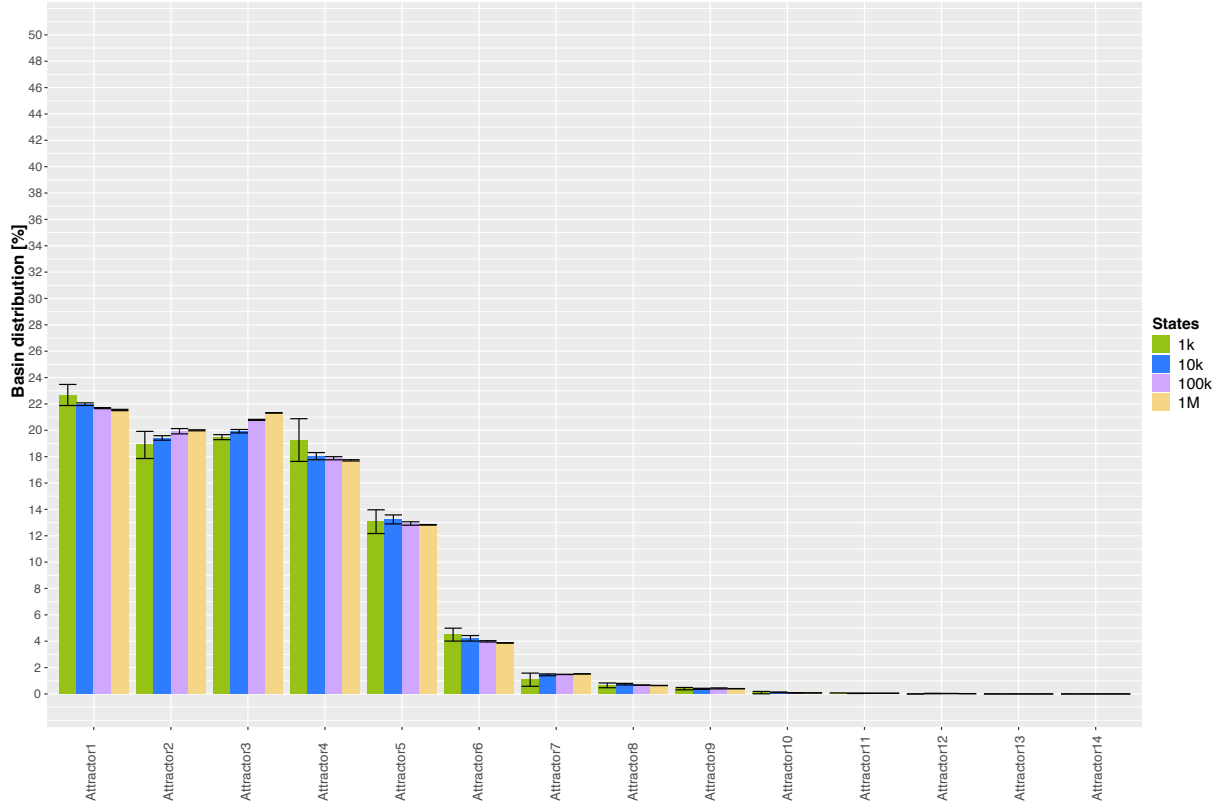
Supplementary Figure 16: mTORC1 and mTORC2 intervention attractor patterns in DAXX loss PanNETs. The attractor landscape of the mTORC1 and mTORC2 intervention on the DAXX loss PanNET network is reported. Attractors are grouped based on their matched phenotypes. Below each attractor the basin size is reported. Activities are reported in the colored boxed. Here, green indicates active (1) and grey indicates inactive (0) genes/proteins.



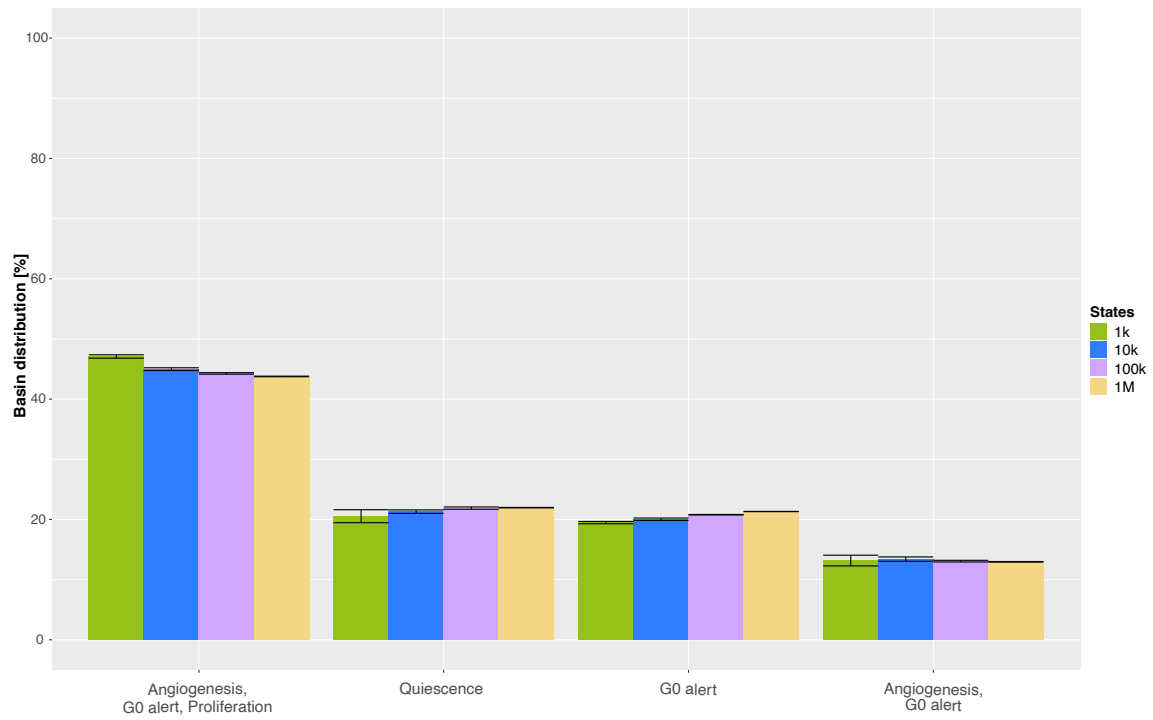
Supplementary Figure 17: mTORC1 and mTORC2 intervention attractor patterns in TSC loss PanNETs. The attractor landscape of the mTORC1 and mTORC2 intervention on the TSC loss PanNET network is reported. Attractors are grouped based on their matched phenotypes. Below each attractor the basin size is reported. Activities are reported in the colored boxed. Here, green indicates active (1) and grey indicates inactive (0) genes/proteins.



Supplementary Figure 18: mTORC1 and mTORC2 intervention attractor patterns in MEN1 loss PanNETs. The attractor landscape of the mTORC1 and mTORC2 intervention on the MEN1 loss PanNET network is reported. Attractors are grouped based on their matched phenotypes. Below each attractor the basin size is reported. Activities are reported in the colored boxed. Here, green indicates active (1) and grey indicates inactive (0) genes/proteins.



Supplementary Figure 19: Basin distribution analysis based on attractors. The basin distribution of the 14 attractors of the MEN1 loss condition is reported above. The abundance of an attractor in the basin was evaluated for 1000 (1k, in green), 10,000 (10k, in blue), 100,000 (100k, in purple), and 1,000,000 (1M, in yellow) randomly drawn starting states. The evaluation has been performed three times for each initial condition. Standard deviations are reported in as bars in the graphs and the height of the histogram represents the means. The initial sampling of starting states does not significantly affect the basin distributions of the attractor landscape.



Supplementary Figure 20: Basin distribution analysis based on grouped phenotypes. The basin distribution of the four retrieved phenotypes of MEN1 loss condition is depicted above. The abundance each in the basin was evaluated for 1000 (1k, in green), 10,000 (10k, in blue), 100,000 (100k, in purple), and 1,000,000 (1M, in yellow) randomly drawn starting states. Attractors matching the reported phenotypes were summed up in their basin abundance. The evaluation has been performed three times for each initial condition. Standard deviations are reported in as bars in the graphs and the height of the histogram represents the means. The initial sampling of starting states does not significantly affect the basin distributions of the final evaluated phenotypes.

DAXX & MEN1	0.143	0.286	0	0.571
MEN1	0.125	0.500	0.375	0
DAXX	0.111	0.444	0.222	0.222
WT	0.824	0.059	0	0.118
	WT	DAXX	MEN1	DAXX & MEN1

DAXX & MEN1	0.143	0.286	0.143	0.429
MEN1	0.125	0.500	0.375	0
DAXX	0.111	0.444	0.222	0.222
WT	0.824	0.059	0	0.118
	WT	DAXX	MEN1	DAXX & MEN1

DAXX & MEN1	0.143	0.143	0	0.714
MEN1	0.125	0.500	0.375	0
DAXX	0.111	0.444	0.222	0.222
WT	0.824	0.059	0	0.118
	WT	DAXX	MEN1	DAXX & MEN1

DAXX & MEN1	0.143	0.143	0.143	0.571
MEN1	0.125	0.500	0.375	0
DAXX	0.111	0.444	0.222	0.222
WT	0.824	0.059	0	0.118
	WT	DAXX	MEN1	DAXX & MEN1

DAXX & MEN1	0.143	0.286	0	0.571
MEN1	0.125	0.375	0.375	0.125
DAXX	0.111	0.444	0.222	0.222
WT	0.824	0.059	0	0.118
	WT	DAXX	MEN1	DAXX & MEN1

DAXX & MEN1	0.143	0.286	0.143	0.429
MEN1	0.125	0.375	0.375	0.125
DAXX	0.111	0.444	0.222	0.222
WT	0.824	0.059	0	0.118
	WT	DAXX	MEN1	DAXX & MEN1

DAXX & MEN1	0.143	0.143	0	0.714
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WT	0.824	0.059	0	0.118
	WT	DAXX	MEN1	DAXX & MEN1

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DAXX	0.111	0.444	0.222	0.222
WT	0.824	0.059	0	0.118
	WT	DAXX	MEN1	DAXX & MEN1

DAXX & MEN1	0.143	0.286	0	0.571
MEN1	0.125	0.375	0.500	0
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WT	0.824	0.059	0	0.118
	WT	DAXX	MEN1	DAXX & MEN1

DAXX & MEN1	0.143	0.286	0.143	0.429
MEN1	0.125	0.375	0.500	0
DAXX	0.111	0.444	0.222	0.222
WT	0.824	0.059	0	0.118
	WT	DAXX	MEN1	DAXX & MEN1

DAXX & MEN1	0.143	0.143	0	0.714
MEN1	0.125	0.375	0.500	0
DAXX	0.111	0.444	0.222	0.222
WT	0.824	0.059	0	0.118
	WT	DAXX	MEN1	DAXX & MEN1

DAXX & MEN1	0.143	0.143	0.143	0.571
MEN1	0.125	0.375	0.500	0
DAXX	0.111	0.444	0.222	0.222
WT	0.824	0.059	0	0.118
	WT	DAXX	MEN1	DAXX & MEN1

Supplementary Figure 21: Alternative equally possible solutions for the multi-class classification experiment (dataset GSE7117851). Alternative solutions depend on the presence of equally voted classes during the majority vote procedure for the experiment. The alternative matrices depicting all possible solution of the multi-class classification experiment are depicted above. Each cell of the matrix reports the probability of a certain group to be assigned to the corresponding one in the matrix. Color intensities (here blue filled boxes) reflect these probabilities, where the higher the probability the more intense the color.

Supplementary Table 1: Boolean functions of the PanNET model. Regulatory interactions of the model are summarised by logic connectives AND ($\wedge$), OR ($\vee$), and NOT ($\neg$). To reduce the complexity of the model, linear interactions are depicted by time delays ($[-2]$). A detailed description of the regulatory Boolean functions is reported with references.

Node; $t + 1$ VEGF	Boolean function; t $(STAT3 \vee HIF1 \vee ET1) \wedge eIFs$	Description eIFs enhances cell proliferation by leading to selective translation of mRNA such as VEGF [2]. VEGF promoter was activated by STAT3 [3]. STAT3 and HIF1 regulate VEGFR transcription simultaneously. HIF1 upregulation leads to increased expression of angiogenic factors such as VEGF [4]. ET1 induces transcription of VEGF [5].
VEGFR	$VEGF \wedge ARF1 \wedge ET1$	VEGF is the ligand of VEGFR and responsible for receptor activation [6]. ARF1-dependent regulates cellular exit of soluble proteins such as VEGFR [7]. ET1 can upregulate the transcription of VEGFR [5].
ARF1	$IGFR \vee MEK \vee ERK \vee RAF$	Activation of ARF1 is downstream of the MAPK signalling cascade. Here ARF1 activation depends on IGFR, MEK, RAF, or ERK [7, 8, 9, 10, 11].
IGF	$(E2F \vee AP1) \wedge ARF1$	AP1 is responsible of inducing IGF expression. E2F binds to the promoter of IGF and induces IGF expression [12]. ARF1 is involved in neuroendocrine secretion and release IGF [7].
IGFR	$(\neg TP53 \wedge (AP1 \vee MYC)) \wedge (IGF \vee mTORC2 \vee FAK1)$	IGF binds to its receptor and activates it [13, 14, 15]. FAK is important for phosphorylation, and the stability of IGR1R [16]. Blocking the interaction of FAK and IGFR precludes activation of IRS [17]. mTORC2 can promote the activation of IGFR by the mTOR specific tyrosin kinase activity [18]. TP53 suppresses the IGFR promoter [19]. TP53 inhibits IGF through induction of IGF-BP3 expression that prevents binding of IGF to IGFR [13]. MYC can promote the expression of IGFR [20]. Likewise, cJUN, which is part of the AP1 transcriptional complex, is found to bind and activate the transcription of IGFR [21, 22, 23].
IRS	$IGFR \wedge \neg S6K \wedge \neg GSK3B$	S6K regulates IRS on transcriptional and translational level, thereby impairing IRS adaptor fusion [15, 4, 24]. Phosphorylation by S6K targets IRS to proteasomal degradation [4]. GSK3B phosphorylates IRS thereby reducing the insulin-stimulated activation [25]. IRS is the major substrate of IGFR [26].
PI3K	$RAS \vee IRS$	RAS activates PI3K [27, 28]. PI3K bound to IRS converts PIP2 into PIP3 [27, 14, 15, 24].
PTEN	$TP53 \wedge \neg GSK3B$	TP53 induces the expression of PTEN [13]. GSK3B phosphorylates PTEN on Thr366 or Ser370 [25]. Treatment with GSK3B inhibitors yield increase in PTEN protein levels [29].

Supplementary Table 1: Boolean functions of the PanNET model. Regulatory interactions of the model are summarised by logic connectives AND ($\wedge$), OR ($\vee$), and NOT ($\neg$). To reduce the complexity of the model, linear interactions are depicted by time delays ($[-2]$). A detailed description of the regulatory Boolean functions is reported with references.

Node; $t + 1$	Boolean function; t	Description
AKT	$GLI1 \wedge ((PI3K \wedge \neg PTEN) \vee mTORC2 \vee NEK2[-2]) \wedge \neg PP2A \wedge \neg MEN1$	GLI1 controls AKT transcription by binding to its promoters [30]. PTEN acts as a negative regulator of PI3K/AKT signaling by reverting PIP3 into PIP2 [31, 27, 4]. PI3K activates AKT via PDK1 [13, 27, 14, 15, 4, 24, 32]. Phosphorylation of AKT by mTORC2 on Ser473 leads to full activation of AKT [13, 27, 14, 15, 4, 24, 32]. PP2A dephosphorylates AKT [33]. PP1 also dephosphorylates AKT [33]. PP1 activity toward AKT-S473 is inhibited by NEK2 [33]. This is included now as a delayed regulation on AKT from NEK2. MEN1 inhibits AKT activity by controlling its subcellular localization [34].
NEK2	$(GLI1 \vee MYC \vee E2F) \wedge (CIP2A \vee S6K)$	GLI1 induces the transcription of NEK2 [35]. Also MYC can transcriptionally activate NEK2 [36]. Similarly, E2F is also a transcriptional regulator of NEK2 [37]. CIP2A enhances NEK2 kinase activity independent from PP2A-PP1 activity [38, 39]. S6K can phosphorylate NEK2 and thereby enhancing its activity [40]
mTORC2	$PI3K \wedge \neg PTEN \wedge \neg S6K$	PIP3 phosphatase activates mTORC2. PTEN degrades PIP3 to PIP2 [13]. S6K inhibits mTORC2 [41].
GLI1	$((MYC \vee STAT3) \wedge \neg MEN1 \wedge \neg TP53) \wedge ((MEK \vee AKT \vee ERK \vee RSK) \wedge (\neg AMPK \wedge (\neg GSK3B \vee (GSK3B \wedge S6K))))$	MYC binds to the promoter of GLI1 and activates its transcription [42, 43, 44, 45]. Similarly, STAT3 can activate GLI1 transcription [46, 47, 48]. MEN1 represses GLI1 expression [49]. TP53 inhibits the transcription, nuclear translocation and protein stability of GLI1 [45]. Constitutively active MEK increases GLI1 activity [45]. MEK and ERK increase the transcriptional activity of GLI1 [45]. MEK and RSK also promote GLI2 nuclear localization and stabilization [45]. AKT also increases transcriptional activity, nuclear localization and protein stability of GLI1 [45]. AMPK inhibits GLI1 via direct binding [50, 51]. S6K enhances activation of GLI1 by preventing its GSK3B mediated degradation [45]. GSK3B induces degradation of GLI1 [45].
GSK3B	$PP2A \wedge \neg AKT \wedge \neg ERK$	PP2A activates GSK3B [33]. AKT inactivates GSK3B by phosphorylation at Ser9 [13, 31, 4]. ERK phosphorylates GSK3B at Thr43 which primes GSK3B for subsequent phosphorylation and inactivation by RSK [24]. Furthermore, ERK phosphorylates Ser9 [52].

Supplementary Table 1: Boolean functions of the PanNET model. Regulatory interactions of the model are summarised by logic connectives AND ($\wedge$), OR ($\vee$), and NOT ($\neg$). To reduce the complexity of the model, linear interactions are depicted by time delays ($[-2]$). A detailed description of the regulatory Boolean functions is reported with references.

Node; $t + 1$	Boolean function; t	Description
PP2A	$\neg\text{CIP2A}$	CIP2A binds to PP2A and inhibits its phosphatase functions resulting in tumorigenic transformation of cells [38, 33, 53, 54].
CIP2A	$\text{ERK}[-2] \vee \text{E2F}$	Treatment of cells with phorbol ester TPA, a well-characterized activator of MEK-ERK signaling pathway, increased CIP2A mRNA expression more than threefold probably via ETS1, a transcription factor downstream of MEK-ERK signaling [53]. E2F induces CIP2A expression [54].
RAS	$(\text{IRS} \vee \text{VEGFR}) \wedge \neg\text{PP2A}$	IGF/IGFR axis also induces activation of MAPK signaling by IRS [14, 28]. VEGFR activates RAS [28]. PP2A inhibits RAS [33].
RAF1	$\text{RAS} \wedge \neg\text{PP2A} \wedge (\neg\text{AKT} \vee (\text{AKT} \wedge \neg\text{NEK2}[-2]))$	RAS activates the RAF1-MEK1/2-ERK1/2 cascade [27, 15, 52]. RAF1 can be regulated by dephosphorylation by PP2A [4]. Inhibitory phosphorylations by AKT on RAF1 are removed by PP1 and/or PP2A during mitogen-stimulated RAF1 activation [24]. PP1 activity toward AKT-S473 is inhibited by NEK2 [33]. Here, we only included NEK2.
MEK	RAF	RAF1 activates MEK via phosphorylation [27, 52, 4].
ERK	$\text{STAT3} \wedge (\text{MEK} \vee \text{RAC1}[-2] \vee \text{ARF1}) \wedge \neg\text{PP2A}$	STAT3 activates ERK promoter [3]. MEK activates ERK via phosphorylation [27, 15, 52, 4]. Alternatively, PAK4 a downstream target of RAC1 can also activate ERK [55]. Expression of ARF1 induces the activation of ERK [10]. PP2A inhibits ERK [33].
RSK	$\text{ERK} \wedge \text{PI3K} \wedge \neg\text{PTEN}$	Activated ERK phosphorylates and activates p90^{Rsk1} [15, 4, 56]. PDK1 phosphorylates RSK [56]. Full activation of RSK1 requires phosphorylation by both ERK and PI3K pathway constituent [57, 58].

Supplementary Table 1: Boolean functions of the PanNET model. Regulatory interactions of the model are summarised by logic connectives AND ($\wedge$), OR ($\vee$), and NOT ($\neg$). To reduce the complexity of the model, linear interactions are depicted by time delays ($[-2]$). A detailed description of the regulatory Boolean functions is reported with references.

Node; $t + 1$	Boolean function; t	Description
TSC	$(TP53 \vee FOXO3) \wedge (AMPK \vee GSK3B \vee REDD) \wedge \neg AKT \wedge \neg ERK \wedge \neg RSK$	TP53 induces the expression of TSC [13]. Similarly, FOXO3 can also induce the expression of TSC [59]. Activated AMPK phosphorylates and activates TSC2 [13, 15, 2, 24, 32]. GSK3B phosphorylates TSC2, thereby activating TSC2 [24]. GSK3B phosphorylates TSC2 only when TSC2 had been previously phosphorylated by AMPK [60]. Thereby GSK3B controls mTOR signaling and S6K [60]. Phosphorylation of TSC2 by AKT releases its inhibitory effect on mTOR [13, 31, 15, 4, 24, 25]. REDD1 releases TSC2 from the association with inhibitory 14-3-3 proteins, which act independently from AKT phosphorylation activity [13, 61]. REDD acts independently of the LKB2-AMPK signaling branch [15]. ERK inhibits TSC1/2 [27, 4, 32]. Activated ERK directly phosphorylates TSC2 at sites that differ from the AKT target sites [15]. RSK-mediated phosphorylation of TSC2 inhibits the TSC1-TSC2 complex [15, 32].
mTORC1	$\neg TSC$	TSC2 exerts GTPase activity to negatively regulate GTP-binding protein RHEB [13, 31, 24, 32].
S6K	$mTORC1 \wedge PI3K \wedge \neg PTEN$	mTORC1 mediates phosphorylation of Thr 389 within the hydrophobic motif, whereas PDK1 is responsible for phosphorylation of the T-loop [13, 33, 27, 15, 56, 26].
AMPK	$(RSK[-2] \vee TP53[-2]) \wedge \neg PP2A \wedge \neg AKT$	LKB1 phosphorylates α -subunit of AMPK on Thr172 activating AMPK [13, 15, 4, 32]. LKB is phosphorylated at Ser431 by p90RSK [62]. Thus we have a linear connection from LKB to RSK to AMPK which we included as delay. Overexpression of Sestrin1 or Sestrin2 led to increases in AMPK activation [32]. TP53 induces expression of Sestrin1/2 [13]. PP2A inhibits AMPK [63, 64]. Insulin activation of AKT increases the phosphorylation of AMPK $\alpha 1/\alpha 2$ at Ser485/491 and inhibits AMPK signaling [65, 66, 67, 68, 69, 70].
REDD	$(HIF1 \vee TP53)$	HIF1 induces the expression of REDD1 and REDD2 [13, 15]. TP53 induces REDD1 expression [13].
TP53	$GSK3B \wedge \neg PP2A \wedge \neg MDM2$	Phosphorylation by GSK3B derepresses TP53 translation [25]. PP2A dephosphorylates TP53 on Ser15, thereby inactivating TP53 [13]. AKT-MDM2-TP53 forms a negative feedback loop to negatively regulate TP53 [13, 31].

Supplementary Table 1: Boolean functions of the PanNET model. Regulatory interactions of the model are summarised by logic connectives AND ($\wedge$), OR ($\vee$), and NOT ($\neg$). To reduce the complexity of the model, linear interactions are depicted by time delays ($[-2]$). A detailed description of the regulatory Boolean functions is reported with references.

Node; $t + 1$	Boolean function; t	Description
MDM2	$(\text{ERK}[-2] \vee \text{TP53}) \wedge (\text{AKT} \vee (\text{DAXX} \wedge \neg \text{RASSF1A}))$	AKT-MDM2-TP53 forms a negative feedback loop to negatively regulate TP53 [13, 31]. AKT phosphorylates MDM2 on Ser166/186 that activates MDM2 to decrease TP53 levels and activity [13, 4] in vitro. MEK, downstream of RAS/ERK can transcriptionally regulate MDM2 [71]. It has recently been shown that DAXX binds to MDM2 and is required for MDM2 activity towards TP53. Also, DAXX associates with RASSF1A and RASSF1C in vivo. Mechanistically, RASSF1A increases MDM2 self-ubiquitination by disrupting MDM2-DAXX-HAUSP interactions [72].
4EBP1	$\neg \text{mTORC1}$	mTORC1 phosphorylates 4E-BP1 [41, 24, 73].
eIFs	$(\text{RSK} \vee \text{AKT} \vee \text{S6K} \vee \text{ERK}[-2]) \wedge \neg 4\text{EBP1}$	RSK, AKT, and S6K phosphorylate eIF4B on Ser422, which promotes eIF4B association with the pre-initiation complex [24]. ERK activates eIFs via MNK [74]. Phosphorylation of 4EBP1 leads to the release of eIF4E, which is then free to associate with eIF4G to stimulate translation initiation [13, 15, 4, 73]. Multiple eukaryotic initiation factors (eIFs) are involved in this process. The heterotrimeric eIF4F consists of the cap-binding protein eIF4E, the scaffolding protein eIF4G, and the licase eIF4A [56].
STAT3	$\text{eIFs} \wedge \text{mTORC1} \wedge \neg \text{SETD7} \wedge \neg \text{DAXX}$	eIF4E is a key component for translation including STAT3 [4]. mTORC1 is one of the kinases that phosphorylate STAT3 at Ser727 and rapamycin reduces STAT3 transcriptional activity [73]. STAT3 transcriptional function is inhibited by dimethylation at K140, which is catalyzed by SETD7 in response to IL-6 signaling, inhibiting STAT3 binding to DNA promoters [75, 76, 77]. DAXX suppresses STAT3 transcription [78, 79].
HIF1	$(\text{STAT3} \vee \text{E2F}) \wedge \text{ERK} \wedge \text{eIFs} \wedge (\neg \text{GSK3B} \vee (\text{GSK3B} \wedge \text{AP1}))$	STAT3 enhances HIF1 transcription and increases HIF1 protein level [80, 81]. E2F activity directly regulates and is required for induction of HIF1 [82]. eIF4E binds at 5'-UTRs of HIF1 and mediate its translation [83]. Phosphorylation from ERK increases HIF1 activity [84, 85, 86]. GSK3B phosphorylates HIF1 and primes it for ubiquitination. cJUN a component of the AP1 complex, can bind HIF1 at its ubiquitination sites and prevent its proteasomal degradation [87, 88].

Supplementary Table 1: Boolean functions of the PanNET model. Regulatory interactions of the model are summarised by logic connectives AND ($\wedge$), OR ($\vee$), and NOT ($\neg$). To reduce the complexity of the model, linear interactions are depicted by time delays ($[-2]$). A detailed description of the regulatory Boolean functions is reported with references.

Node; $t + 1$	Boolean function; t	Description
FOXO1	$((\neg \text{AKT} \wedge \neg \text{SKP2}) \vee (\text{AKT} \wedge \text{MEN1}) \vee (\text{SKP2} \wedge \text{MEN1})) \wedge \neg \text{mTORC2}$	AKT phosphorylates FOXO1 [33, 89, 90] at three distinct sites, Thr24, Ser256 and Ser319. Phosphorylation of FOXO1 in the nucleus leads to export into the cytoplasm and thus repression of its transcriptional activity [91, 92, 90]. SKP2 inhibits FOXO1 through induction of its degradation [93]. MEN1 represses ubiquitination of FOXO1 protein and AKT phosphorylation. MEN1 also stabilizes FOXO1 by repressing FOXO1 degradation mediated by S-phase kinase-associated protein 2 (SKP2), an E3 ubiquitin ligase [94]. mTORC2 controls FOXO1 acetylation through inhibition of HDAC2A class [95].
FOXO3	$\neg \text{AKT} \wedge \neg \text{mTORC2}$	AKT phosphorylates FOXO3 [33, 89]. mTORC2 controls FOXO acetylation through inhibition of HDAC2A class [95].
SLUG1	$\neg \text{GSK3B} \wedge (\text{ERK}[-2] \vee \text{GLI1}) \wedge (\neg \text{DAXX} \vee (\text{DAXX} \wedge \text{HIF1}))$	SLUG1 bound to DAXX cannot inhibit the CDH1 promotor anymore, thus is inactive; when HIF1 is present instead, it can bind DAXX and prevent SLUG1 inhibition of CDH1 activity [96]. GSK3B controls EMT by chip-mediated degradation of SLUG1 [97]. ERK can control the expression of SLUG1, putatively via SP1 [98, 99]. GLI1 can induce transcription of SLUG1 also in BON-1 cells [100, 101, 102].
CDH1	$\neg \text{SLUG1} \vee \text{PDX1}$	SLUG1 inhibits the CDH1 promotor [103, 102]. PDX1 directly binds and activates CDH1 transcription [104].
MYC	$(\text{ERK}[-2] \vee (\text{CTNNB1} \wedge \text{RAC1})) \wedge \neg \text{FOXO3} \wedge \neg \text{FOXO1} \wedge \neg \text{MEN1} \wedge \neg \text{GSK3B} \wedge (\neg \text{PP2A} \vee \text{CIP2A})$	ERK controls activation of MYC via upregulation of mRNA levels [105, 106]. GSK3B enhances Thr58 phosphorylation and ubiquitination of MYC [107]. CTNNB1 presence in the nucleus, where it can induce MYC expression, controlled by RAC1 [108]. On the opposite way, MEN1 shuffles CTNNB1 from the nucleus to the cytosol [109, 110, 94]. MEN1 can also control expression of MYC [49]. FOXO1 and FOXO3 can repress MYC by inducing two miRNAs [95]. As part of the destruction complex, GSK3B inhibits the induction of MYC by CTNNB1 [111]. If not bound to cancerous inhibitor of PP2A (CIP2A), PP2A degrades MYC [112, 113].

Supplementary Table 1: Boolean functions of the PanNET model. Regulatory interactions of the model are summarised by logic connectives AND ($\wedge$), OR ($\vee$), and NOT ($\neg$). To reduce the complexity of the model, linear interactions are depicted by time delays ($[-2]$). A detailed description of the regulatory Boolean functions is reported with references.

Node; $t + 1$	Boolean function; t	Description
CTNNB1	$\neg \text{GSK3B} \vee (\text{GSK3B} \wedge \neg \text{SETD7}) \vee (\text{GSK3B} \wedge \text{CDH1})$	GSK3B phosphorylates CTNNB1 inducing its proteasomal degradation [114, 115]. SETD7 methylates CTNNB1 at K180, which strengthens the interaction of CTNNB1 with GSK3B [75]. CTNNB1 can be sheltered from GSK3B degradation activity when bound to CDH1 at the cellular membrane. In this case, it accomplished its role in tight junctions and can not be exported in the nucleus to activate transcription of its target genes [116].
Tight Junctions (TJ)	$\text{CDH1} \wedge \text{CTNNB1} \wedge (\neg \text{IQGAP1} \vee ((\text{IQGAP1} \wedge (\text{RAC1} \vee \text{MEN1}))))$	CDH1 and CTNNB1 are essential components of tight junctions [117, 118]. The presence of CTNNB1 at the membrane is also determined by its shuffling from and to the nuclei. In this context, RAC1 promotes CTNNB1 shuffling to the nuclei, while MEN1 promotes its presence in the cytoplasm [108, 109, 110, 94]. In addition, the binding of IQGAP1 to CTNNB1 abrogates the binding of the CTNNB1/CDH1 complex to a-catenin and thus, leads to decreased adhesion [117, 118]. IQGAP1-mediated inhibition of adhesion can be relieved by binding of RAC1-GTP to IQGAP1, which displaces IQGAP1 from CTNNB1 [117, 118, 119]. Also, MEN1 can cause a similar effect to RAC1 by competitively binding IQGAP1 [117].
RASSF1A	$\neg \text{SKP2}$	RASSF1A undergoes ubiquitin-mediated degradation by SKP2 [120, 72].
MEN1	FOXO1	MEN1 expression is induced by FOXO1 [91, 94, 34].
p27	$(\text{MEN1} \vee \text{FOXO3} \vee \text{PP2A}) \wedge \neg \text{SKP2}$	p27 can be induced by MEN1 [121, 122, 123, 124, 125, 126, 127]. Also FOXO3 can transcriptionally induce p27 [128, 129]. PP2A can also induce accumulation of p27 independent from the AKT pathway [130, 131]. SKP2 induces p27 degradation [132, 132].
p18	MEN1	MEN1-dependent histone methylation maintains the expression of p18 [122, 133, 123, 124, 125, 126, 127].
p21	$(\text{TP53} \vee \text{RSK}[-2] \vee \text{MEN1}) \wedge \neg \text{SKP2} \wedge \neg \text{GLI1}$	LKB1, directly downstream of RSK, can also transcriptionally induce the expression of p21 [134, 135]. TP53 induces p21 expression [136, 72]. MEN1 can also induce p21 expression [137]. SKP2 phosphorylates p21 and prompts it for degradation [138]. p21 expression is upregulated in cells with decreased GLI1 expression [139].

Supplementary Table 1: Boolean functions of the PanNET model. Regulatory interactions of the model are summarised by logic connectives AND ($\wedge$), OR ($\vee$), and NOT ($\neg$). To reduce the complexity of the model, linear interactions are depicted by time delays ($[-2]$). A detailed description of the regulatory Boolean functions is reported with references.

Node; $t + 1$	Boolean function; t	Description
CCND1	$(MYC \vee (CTNNB1 \wedge RAC1 \wedge \neg MEN1)) \wedge \neg p18 \wedge \neg RASSF1A \wedge \neg GSK3B$	MYC can induce the expression of CCND1 [140, 141, 142]. CTNNB1 presence in the nucleus, where it can induce CCND1 expression, is controlled by RAC1 [108]. On the opposite way, MEN1 shuffles CTNNB1 from the nucleus to the cytosol [109, 110, 94]. p18 inhibits CCND1 activity by inhibiting binding to CDK4 and CDK6 [143]. GSK3B, has been shown to phosphorylate CCND1 on Thr286 in vitro, and is postulated to regulate CCND1 levels and intracellular distribution [144]. RASSF1A inhibits accumulation of CCND1 [145].
RB	PP2A	PP2A dephosphorylates RB, leading to its activation [146, 147, 148, 149, 150].
E2F	$(\neg RB \vee (RB \wedge CCND1) \vee (RB \wedge PDX1)) \wedge \neg p21$	Phosphorylation of RB by CCND1 release E2F [151, 152, 153, 154]. RB can also bind and stabilize PDX1 at the same conserved site at which RB interacts with E2Fs [155]. Thus PDX1 binding to RB competes with its binding to E2Fs [155]. p21 suppresses the activity of E2F-responsive promoters (dihydrofolate reductase and CDC2) [156].
CCNE1	$E2F \wedge \neg p21 \wedge \neg p27$	E2F1 promotes CCNE1 transcription and progression from the G1 to S phase of the cell cycle [152, 153, 154]. p27 can inhibit CCNE1 by binding CDK4 [157, 158]. p21 inhibits CCNE1-CDK2 [159].
DAXX	$MEN1 \wedge ERK[-2]$	MEN1 binds and regulates DAXX activity at gene promoters [160, 91]. DAXX expression can be induced by ETS1 a transcription factor downstream of ERK [161].
ET1	$(HIF1 \wedge AP1) \vee (CTNNB1 \wedge RAC1 \wedge \neg MEN1)$	Hypoxia is one of the most potent inducers of ET1 [162, 5]. Mutations of HIF1 or AP1 in the ET1 promoter eliminate activation by hypoxia [162]. CTNNB1 can induce the expression of ET1 via binding of TCF4 to the ET1 promoter [163, 164]. CTNNB1 presence in the nucleus, where it can induce CCND1 expression, is controlled by RAC1 [108]. On the opposite way, MEN1 shuffles CTNNB1 from the nucleus to the cytosol [109, 110, 94].
SKP2	AKT	Inactivation of AKT1 decreases SKP2 mRNA levels [165].

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Node; $t + 1$	Boolean function; t	Description
FAK1	$(ET1 \vee (IGFR \wedge ARF)) \wedge \neg RAF1$	ARF1 is essential for the EGF-mediated activation of FAK1 [166, 11]. ET1 signaling increases the activation of FAK1 [5, 167]. The ability of FAK1 to mediate integrin signaling in the regulation of cell cycle progression depends on the phosphorylation of Tyr397, which implies a functional significance for the formation of FAK1 signaling complexes with SRC, phosphatidylinositol-3-kinase (PI3K) and GRB7. There is a FAK1 mutant, D395A, that selectively disrupts FAK1 binding to PI3K, but allows FAK1 association with SRC. SRC-dependent association of FAK with Grb2 and p130Cas are both required for the regulation of cell cycle progression by FAK1 [168]. Overexpressed RAF1 increases phosphorylation of FAK1 at the site of Tyr407, the negative regulator of FAK1 kinase activity [169, 170]. Suppression of RAF1 in BON-1 cells induced FAK1 activation as well as increased invasion and aggressiveness, whereas MEK inhibition did not affect migration. Moreover, PanNET cells are known to have low levels of RAF1 activation [169, 170].
RAC1	$(FAK1 \vee PI3K \vee mTORC1)$	RAC1 is activated by receptor tyrosine kinases such as PI3K [171, 172]. RHO-GEF downstream of FAK1/Paxillin activates RAC [5]. FAK1 activates and translocates RAC1 for focal adhesion [173, 174]. Disruption of mTORC1 and mTORC2 by inhibiting Raptor and Rictor, respectively, inhibits the activity of RHOA and RAC1. In addition, mTORC1 was also shown to control the translation of RHOA and RAC1 mRNAs via 4E-BP1 and p70S6K [175, 176].
IQGAP1	$\neg GSK3B$	Inhibition of GSK3B frees IQGAP1 to regulate RAC1 [177].
PDX1	$((RB \wedge CCND1) \vee RB \vee ERK) \wedge \neg GSK3B \wedge \neg MEN1$	In pancreatic cells the glucose-induced response is dependent upon ERK1/2 phosphorylation of a subset of transcription factors, that include PDX1 [178]. RB stabilizes PDX1 and regulates its half-life [155]. Besides, PDX1 preferentially interacts with phosphorylated forms of RB, particularly via the Cdk4-dependent phosphorylation of the Ser780 residue of RB [178]. GSK3B phosphorylates PDX1 prompting it to proteosomal degradation [179, 180]. MEN1 can repress the expression of PDX1 [181].
SETD7	PDX1	SETD7 is activated at transcription level by PDX1 [182].

Supplementary Table 1: Boolean functions of the PanNET model. Regulatory interactions of the model are summarised by logic connectives AND ($\wedge$), OR ($\vee$), and NOT ($\neg$). To reduce the complexity of the model, linear interactions are depicted by time delays ($[-2]$). A detailed description of the regulatory Boolean functions is reported with references.

Node; $t + 1$	Boolean function; t	Description
AP1	$(\text{ERK} \vee (\text{CTNNB1} \wedge \neg \text{GSK3B} \wedge \neg \text{MEN1})) \wedge \text{RAC1}[-2]$	ERK increases the expression of AP1 transcription factor [183, 184, 185]. CTNNB1 can also transcriptionally induce AP1 [186, 187, 188]. MEN1 shuffles CTNNB1 from the nucleus to the cytosol [109, 110, 94]. GSK3B-triggered c-JUN phosphorylation inhibits AP1 [52]. JNK mediates the activation of AP1 via its phosphorylation (here RAC1[-2]) [189, 190, 191].

Supplementary Table 2: List of details on the model components.

Node	Name	Compartment	Function
VEGF	vascular endothelial growth factor	extracellular	growth factor
VEGFR	vascular endothelial growth factor receptor	plasma membrane	signal transduction
ARF1	ADP ribosylation factor 1	cytosol	small GTPase/ membrane trafficking
IGF1	insulin like growth factor 1	extracellular	growth factor
IGFR	insulin like growth factor 1	plasma membrane	signal transduction
IRS	insulin receptor substrate	cytosol	signal transduction
PI3K	phosphatidylinositol 3-kinase	cytosol	kinase
PTEN	phosphatase and tensin homolog	cytosol	phosphatase
AKT	AKT serine/threonine kinase	cytosol	kinase
NEK2	NIMA related kinase 2	cytosol	kinase
mTORC2	mechanistic target of rapamycin kinase complex 2	cytosol	kinase
GLI1	GLI family zinc finger 1	nucleus	transcription factor
GSK3B	glycogen synthase kinase 3 beta	cytosol	kinase
PP2A	protein phosphatase 2A	cytosol	phosphatase
CIP2A	cellular inhibitor of PP2A	cytosol	phosphatase inhibitor (binding)
RAS	rat sarcoma	cytosol	GTPase/ signal transduction
RAF	raf proto-oncogene	cytosol	kinase
MEK	mitogen activated protein kinase kinase	cytosol	kinase
ERK	mitogen activated protein kinase	cytosol	kinase
RSK	ribosomal protein S6 kinase	cytosol	kinase
TSC	TSC complex	cytosol	signal transduction
mTORC1	mechanistic target of rapamycin kinase complex 1	cytosol	kinase
S6K	ribosomal protein S6 kinase B1	cytosol	kinase
AMPK	protein kinase AMP-activated	nucleus	kinase
REDD	DNA damage inducible transcript	cytosol	signal transduction
TP53	tumor protein p53	nucleus & cytosol	transcription factor
MDM2	MDM2 proto-oncogene	nucleus & cytosol	E3 ubiquitin-protein ligase
4E-BP1	eukaryotic translation factor 4E binding protein 1	cytosol	repressor of translation initiation
eIF's	eukaryotic translation initiation factor 4E	cytosol	activator of protein synthesis
STAT3	signal transducer and activator of transcription 3	cytosol & nucleus	signal transduction & transcription factor
HIF1	hypoxia inducible factor 1	cytosol & nucleus	transcription factor
FOXO1	forkhead box O1	cytosol & nucleus	transcription factor
FOXO3	forkhead box O3	cytosol & nucleus	transcription factor
SLUG1	snail family transcription repressor 2	nucleus	transcription factor
CDH1	E-cadherin	plasma membrane	cell adhesion
MYC	MYC proto-oncogene	nucleus	transcription factor
RASSF1A	Ras association domain family member 1	nucleus & cytosol	signal transduction
MEN1	menin 1	cytosol & nucleus	transcriptional factor
p27	cyclin dependent kinase inhibitor 1B	nucleus & cytosol	CDK inhibitor
p18	cyclin dependent kinase inhibitor 2C	nucleus & cytosol	CDK inhibitor
p21	cyclin dependent kinase inhibitor 1A	nucleus & cytosol	CDK inhibitor
CCND1	cyclin D1	nucleus	kinase complex
RB	RB transcriptional corepressor	nucleus	signal transduction
E2F	E2F transcription factor	nucleus	transcription factor
CCNE1	cyclin E1	nucleus	kinase complex
DAXX	death domain associated protein	cytosol & nucleus	transcription factor
ET1	endothelin 1	cytosol	membrane trafficking

SKP2	S-phase kinase associated protein 3	cytosol & nucleus	E3 ubiquitin-protein ligase
FAK1	protein tyrosine ligase	cytosol	kinase
RAC1	rac family small GTPase 1	cytosol	cell adhesion
IQGAP	IQ motif containing GTPase activating protein 1	cytosol & plasma membrane	cell adhesion
PDX1	pancreatic and duodenal homeobox 1	nucleus	transcription factor
SETD7	SET domain containing 7	nucleus	histone methyltransferase
AP1	AP1 transcription factor	nucleus	transcription factor

Supplementary Table 3: Comparison of mutated attractor landscapes with knowledge on PanNETs. Each simulated mutated condition (WT, DAXX loss, TSC loss, and MEN1 loss) is summarized in terms of attractor matched phenotypes. Matched information from PanNETs mouse models and patient cohorts is reported and matched, when available. Note that, due to the rarity of PanNETs, patients cohorts for specific mutations collect a rather limited number of patients.

Mutation	Attractor matched phenotypes	Mouse model information	Patient cohort information
WT	99% quiescent, 1% angiogenesis, proliferation, detachment	–	WT PanNETs showed better prognosis compared mutated ones [192].
DAXX	98.9% quiescent, 1.1% angiogenesis, proliferation, detachment 0.1% G0 alert, detachment	Conditional Pdx1-cre driven DAXX inactivation could indicate that DAXX alone has limited effect on pancreatic development and function. However, an alteration of transcriptome was observed, creating permissive chromatin states favoring further mutations and progression [193]. Another mouse model for DAXX inactivation showed comparable results on the tolerability of DAXX loss in the pancreas [194]	Patients in showing DAXX loss mutations show contrasting results, [195] with certain cohorts associating DAXX loss to positive prognosis [196, 197, 198, 199], and others to negative prognosis [200, 201, 202, 198]. However, in accordance to the mouse models results, DAXX loss has been associated to chromosomal instability, specifically altered telomere lengthening, in patient cohorts [196, 201, 202, 198]. Differences observed in DAXX patients cohorts have been hypothesized to be imputed to factors such of the metastatic status of the patients, or the evaluation of histopathological results [195].
TSC	99% G0 alert, 1% angiogenesis, proliferation, detachment	–	Genetic loss of TSC in most of the cases does not correlate with aggressive PanNETs [203].
MEN1	22% quiescence, 20% G0 alert, 13% angiogenesis, G0 alert, 44% angiogenesis, proliferation, detachment	Mouse models with heterogeneous loss of MEN1 develop multiple endocrine tumors, but they do not develop up to carcinoma stages [204].	MEN1 is the most frequently mutated gene in human PanNETs, associated with the presence of multiple neuroendocrine tumors [196].

Supplementary Table 4: Model validation. The activity levels of model compounds compared to literature descriptions or gene expression datasets. This table is the reference for Figure 5 of the main.

Pathway	Node	Model-based activity	Validation
Angiogenesis	VEGF	active	[205, 206]
Angiogenesis	VEGFR	active	[205, 206]
Angiogenesis & cell cycle	HIF1	partially active	[205]
Angiogenesis & MAPK signaling	ARF1	active	[207]
MAPK signaling	FAK1	active	[208]
MAPK signaling	RAF	constant	[209, 210]
MAPK signaling	ERK	partially active	[211]
MAPK signaling	NEK2	partially active	[212, 213]
MAPK signaling & PI3K/AKT signaling	GLI1	active	[102]
MAPK signaling & PI3K/AKT signaling	IGF	active	[214]
MAPK signaling & PI3K/AKT signaling	IGFR	active	[215, 216]
MAPK signaling & PI3K/AKT signaling	PP2A	inactive	[33]
MAPK signaling & PI3K/AKT signaling	CIP2A	active	[214]
PI3K/AKT signaling	PI3K	active	[217]
PI3K/AKT signaling	AKT	active	[211, 208, 218, 219]
PI3K/AKT signaling	PTEN	constantly inactive	[220, 221]
PI3K/AKT signaling	GSK3B	inactive	[222, 223]
PI3K/AKT signaling	FOXO1	inactive	[224]
PI3K/AKT signaling	FOXO3	inactive	[225]
PI3K/AKT signaling & cell cycle	RASSF1A	inactive	[226, 227]
Cell cycle	MDM2	partially active	[228, 229]
Cell cycle	TP53	constant	[228, 229]
Cell cycle	MYC	active	[230, 231]
Cell cycle	MEN1	inactive	[232, 233]
Cell cycle	p27	inactive	[234, 235]
Cell cycle	p21	inactive	[236]
Cell cycle	p18	inactive	[234]
Cell cycle	CCND1	active	[211, 237]
Cell cycle	RB	inactive	[238]
Cell cycle	E2F	active	[214]
Cell cycle	CCNE1	active	[214]
Cell cycle	DAXX	inactive	[239]
mTORC signaling	mTORC1	active	[240]
mTORC signaling	TSC	inactive	[220]
mTORC signaling	mTORC2	constant	[240]
mTORC signaling	STAT3	partially active	[241]
Cell adhesion	CDH1	partially active	[214]
Cell adhesion & cell cycle	CTNNB1	active	[242]
Cell adhesion & cell cycle	SLUG	active	[221, 243]
Cell adhesion & cell cycle	PDX1	partially inactive	[244, 245]

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